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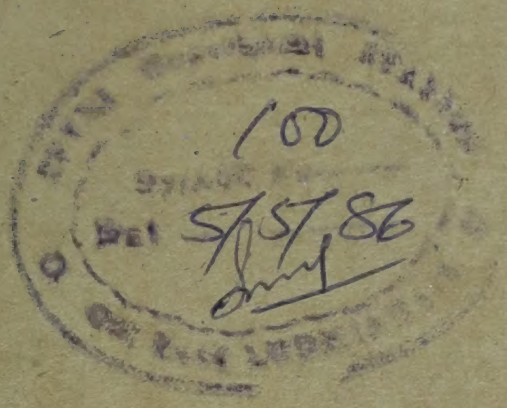

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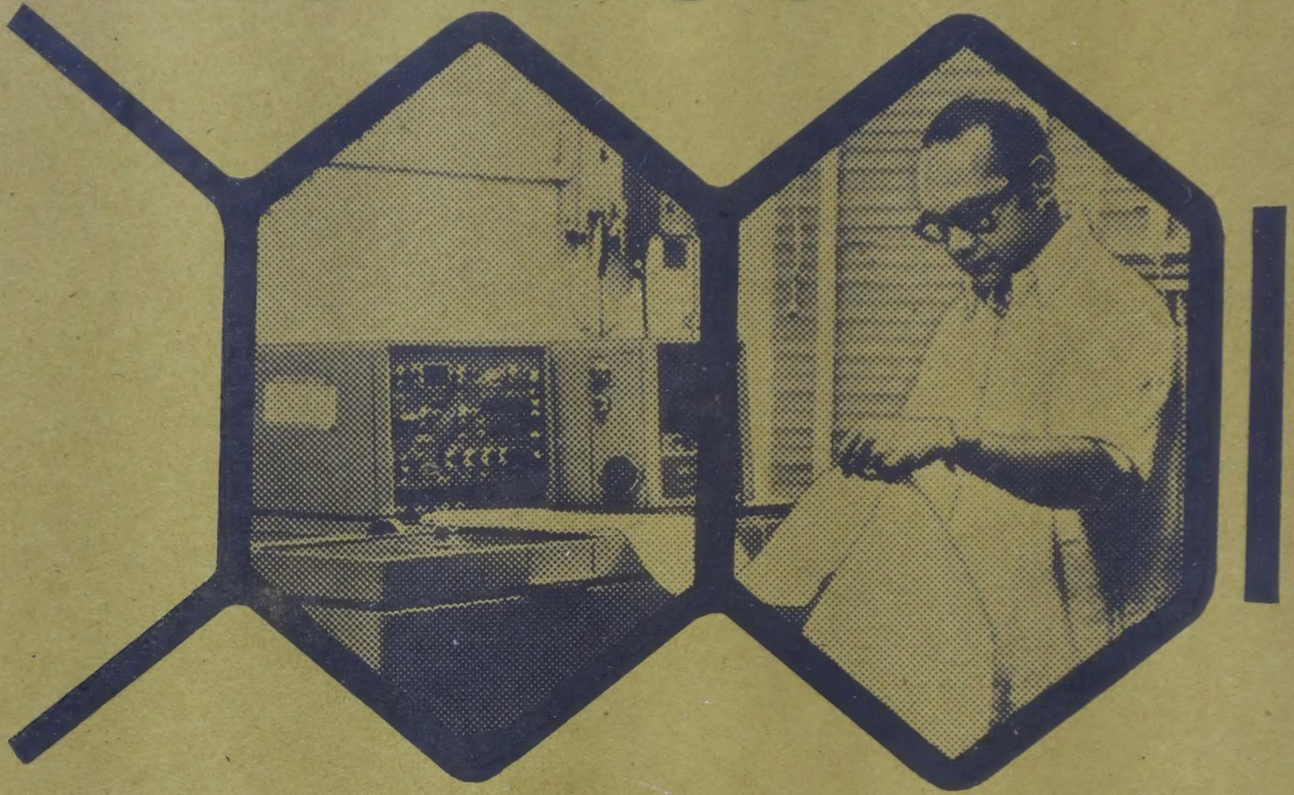

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Papers

New Triterpenes from *Barringtonia speciosa* Forst

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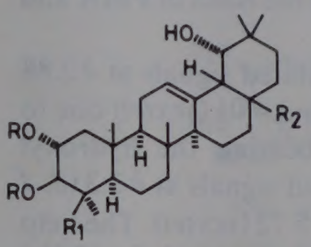
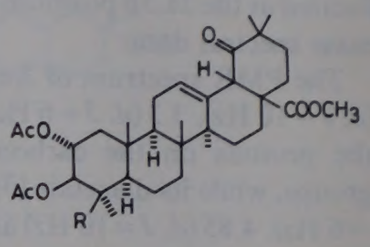
Three new triterpene acids, viz. bartogenic acid, anhydrobartogenic acid and 19-epibartogenic acid, have been isolated from the fruits of *Barringtonia speciosa*. The structures and stereochemistry of these acids have been established as 2α,3β, 19α-trihydroxyolean-12-ene-24,28-dioic acid (**1**), 2α,3β-dihydroxyolean-12,18-diene-24,28-dioic acid (**20**) and 2α,3β,19β-trihydroxyolean-12-ene-24,28-dioic acid (**22**) respectively based on ^1H, ^{13}C NMR and mass spectral data, chemical reactions and finally conversion of dimethyl bartogenate (**2**) into the known triterpene, methyl sericiate (**8**).

The genus *Barringtonia* belongs[1] to the natural order Lecythadaceae and tribe Myrtaceae and consists of twenty species distributed from tropical Africa to Farmosa, Polynesia and Northern Australia. Of these, *B. acutangula* Gaerth, *B. racemosa* Roxb. and *B. speciosa* Forst (syn: *B. asiatica* Kurz) are commonly found in India and used[2] as important drugs in the folk medicine. Several novel triterpenes were reported from *B. acutangula*[3] and *B. racemosa*[4]. Chemical examination of the constituents of *B. speciosa* has not been investigated despite its reputation as a traditional drug in the indigenous medicine. The berries of *B. speciosa* are locally used as abortifacients.

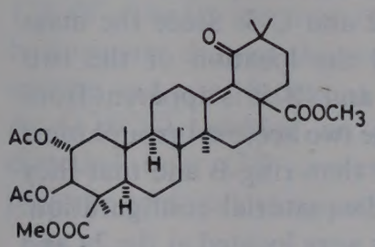
Extraction of the powdered and defatted fruits of *B. speciosa* with chloroform afforded an acidic sapogenin mixture which was esterified with diazomethane and separated into the dimethyl esters of bartogenic, anhydrobartogenic and 19-epi-bartogenic acids. The pure acids were obtained by alkaline hydrolysis of these esters. Further extraction with methanol yielded a mixture which was saponified and separated into acidic and neutral constituents. The acidic components were found to be identical with those obtained from the chloroform extract. The acids and their dimethyl esters answered positive Liebermann-Burchard and Salkowsky tests characteristics of pentacyclic triterpenes. The esters gave yellow colouration with tetranitromethane indicating unsaturation.



(1) R = H ; R_1 = COOH
(2) R = H ; R_1 = $COOCH_3$
(3) R = Ac ; R_1 = $COOCH_3$
(16) R = Ac ; R_1 = CH_2OAc



(4) R = $COOCH_3$
(14) R = CH_2OH



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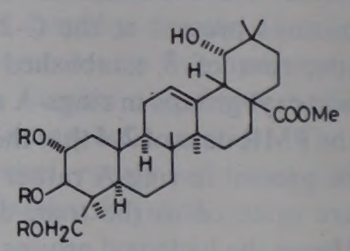


(8) R = H
(9) R = Ac

Bartogenic acid (**1**)

It analysed for $C_{30}H_{46}O_7$ (M^+, 518), m.p. 318°, $[\alpha]_D^{25}$, 118°, gave a dimethyl ester (**2**), $C_{32}H_{50}O_7$ (M^+, 546), m.p. 275-78° and a dimethyl ester diacetate (**3**), $C_{36}H_{54}O_9$ (M^+, 630), m.p. 196°. Further acetylation of **3** with acetic anhydride in perchloric acid resulted in an amorphous triacetate free from hydroxyl absorption in the IR spectrum. **3** resisted hydrogenation and yielded a monoepoxide. These reactions clearly established the presence of two carboxyl groups, three hydroxyls of which one is hindered and a double bond in **1**. The PMR spectrum of **3** displayed signals due to six tertiary methyl groups, two acetylmethyl groups, two carbomethoxy groups, three protons on a carbon bearing the oxygen substituents and a vinylic proton. The mass spectrum of **3** exhibited an intense peak at *m/z* 278 due to retro-Diels-Alder fragmentation of ring-C, characteristic of the Δ^{12}-oleananes[5]. The fragmentation pattern clearly established that the rings-A and -B contained the two acetoxyl and one carbomethoxyl groups while rings-C and -D had the other carbomethoxyl and the hindered hydroxyl substituents.

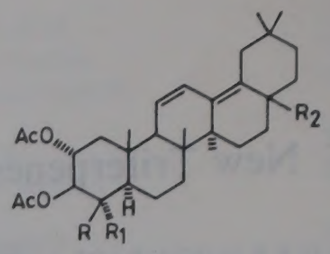
Oxidation of **3** with Jones[6] reagent afforded a β,γ-unsaturated ketone (**4**) which was isomerised[6] to the

α,β-unsaturated ketone (**5**) with methanolic potassium hydroxide. This established the relationship between the hindered hydroxyl group and the double bond as homoallylic in the parent acid (**1**). Dehydration of **3** with $POCl_3$-pyridine afforded dimethyl-diacetyl anhydrobartogenate (**6**), a *cis*-diene which readily isomerised to the stable transoid diene (**7**) having the typical UV spectrum [244, 252, 261 nm (ε, 19950, 25120, 16600)], characteristic of the 11, (18)-diene system[7] thus confirming the position of the hindered hydroxyl group as 19α-axial.

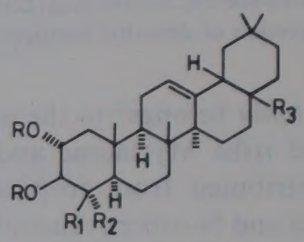
Dimethyl bartogenate (**2**) rapidly consumed one mol of periodic acid and afforded a diosphenol on oxidation with CrO_3-pyridine, indicating[6] the presence of a vicinal *trans*-diol system which was located at the 2α,3β positions on the basis of PMR and mass spectral data.

The PMR spectrum of **2** exhibited signals at δ 2.88 (*d*, $J=10$ Hz), 3.3 (*d*, $J=6$ Hz) and 4.01 (*sextet*) due to the protons on the carbons bearing the hydroxyl groups, while its diacetate (**3**) had signals at δ 3.3 (*d*, $J=6$ Hz), 4.85 (*d*, $J=10$ Hz) and 5.72 (*sextet*). The keto compound (**4**) showed resonances at 4.85 (*d*, $J=10$ Hz) and 5.72 (*sextet*). The doublet at δ 3.3 in **2** and **3** was attributed to the 19β-proton since this was absent in the **4**. The sextet ($d \times t$) at δ 5.72 in **3** and **4** has been attributed to the proton flanked by a methine and methylene protons. These data conclusively established the *trans*-diaxial relationship for the two protons present at the C-2 and C-3. Since the mass spectrum of **3** established the location of the two acetoxyl groups in rings-A and -B, it is apparent from the PMR data of **2-4** that the two acetoxyl groups must be present in ring-A rather than ring-B and that they are oriented in the *trans*-diequatorial configuration. Hence the hydroxyl groups were located at the 2α and 3β positions in **2**. Further the 2β-proton of **3** was considerably deshielded and appeared at δ 5.72 unlike in the other triterpenes[8] having the 2α,3β-dihydroxy stem. This appreciable deshielding is due to the presence of a suitably positioned carbomethoxyl group which is located at C-24′, having the axial configuration. These results clearly establish the structure of bartogenic acid as 2α,3β,19α-trihydroxyolean-12-en-24,28-dioic acid (**1**) in analogy with other triterpenes[6,9,10,11]. This structure is confirmed from the following experiments.

Reduction of dimethyl diacetylbartogenate (**3**) with vitride reagent (70% solution of sodium bis-2-methoxyaluminium hydride in benzene) afforded a monoester (**8**), $C_{31}H_{50}O_6$ (M^+ 518), m.p. 165° which gave a triacetate (**9**), m.p. 175°. The mass spectrum of **9** showed an intense peak at *m/z* 278 due to retro-Diels-Alder fragmentation suggesting the presence of a carbomethoxyl and hydroxyl groups in rings-D and -E, respectively as in **3**. This clearly established that the other carbomethoxy group of **3** is selectively reduced to the hydroxymethyl group. Further **8** has been found to be identical with methyl sericiate[12] by comparison with an authentic specimen (IR, ^{1}PMR; ^{13}C NMR, MS and ORD) thus confirming the structure and stereochemistry of bartogenic acid (**1**).



(7) $R = R_2 = COOMe$; $R_1 = CH_3$
(12) $R = CH_2OAc$; $R_1 = CH_3$; $R_2 = COOCH_3$
(13) $R = Me$; $R_1 = CH_2OAc$; $R_2 = COOCH_3$
(17) $R = R_2 = CH_2OAc$; $R_1 = CH_3$
(18) $R = Me$; $R_1 = R_2 = CH_2OAc$



(10) $R=H$; $R_2 = CH_2OH$; $R_1 = CH_3$; $R_3 = COOCH_3$
(11) $R=OAc$; $R_2 = CH_2OAc$; $R_1 = CH_3$; $R_3 = COOCH_3$
(15) $R=H$; $R_1 = CH_2OH$; $R_2 = CH_3$; $R_3 = COOCH_3$
(19) $R=H$; $R_1 = CH_3$; $R_2 = R_3 = CH_2OAc$.

The PMR spectrum of **9** displayed a two-proton singlet at δ 4.18 assignable to 24-CH_2OAc. However, in the PMR spectrum of methyl triacetyl arjunolate (**11**) the 23-CH_2OAc protons appeared as a pair of doublets at δ 3.65 ($J=11$ Hz) due to methylene nonequivalence[13]. This appreciable difference in the chemical shifts and the coupling patterns between the protons of equatorial and axial CH_2OAc groups at C-4 is significant and can be used to establish the configuration of these substituents in pentacyclic triterpenes.

Dehydration of **9** with $POCl_3$-pyridine followed by isomerisation afforded a diene (**12**), m.p. 144°, which was different (IR, PMR) from the diene (**13**), obtained by the SeO_2 oxidation of methyl triacetylarjunolate (**11**), m.p. 254°, indicating the configurational change of the substituents in **12** and **13**. This was confirmed from the CD spectra of the tribenzoates obtained from **12** and **13** which showed[14] opposite Cotton effect curves.

Oxidation of **9** with CrO_3-pyridine yielded a β,γ-unsaturated ketone (**14**), m.p. 200-201° which was subjected to a modified[15] Wolf-Kishner reduction and

the resulting compound (**15**), m.p. 140° was isomeric but different from methyl arjunolate (**10**).

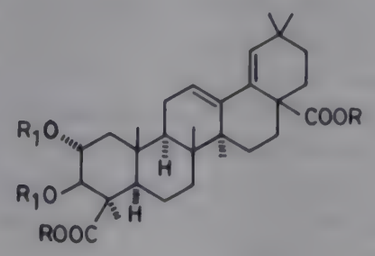
Reduction of dimethyl diacetyl bartogenate (**3**) with lithium aluminium hydride followed by acetylation gave the tetraacetate (**16**), m.p. 122-23° which was dehydrated and isomerised to the diene (**17**), m.p. 129°. This diene (**17**) was isomeric but different from the diene (**17**), m.p. 196°, obtained from tetraacetyl barringtogenol (**19**). The PMR spectrum of the diene (**17**) exhibited a two-proton singlet at δ 4.1 for the 24-CH_2OAc protons while the two protons due to 23-CH_2OAc, appeared at 3.65 as a quartet in the diene (**18**) thus confirming the configurational change at C-4 in these compounds.

The above chemical reactions, spectral data together with the conversion of **3** into methyl sericiate (**8**) clearly established the structure and stereochemistry of bartogenic acid as 2α,3β,19α-trihydroxyolean-12-en-24,28-dioc acid as represented in (1).

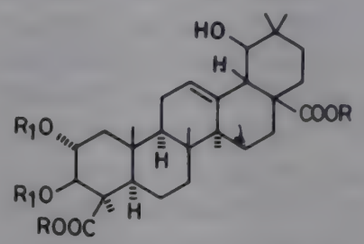
Anhydrobartogenic acid (**20**)

This amorphous compound was isolated as its dimethyl ester (**21**), $C_{32}H_{48}O_6$ (M^+ 528), m.p. 270-72° and gave a diacetate (**6**), m.p. 140-42° identical with dimethyl diacetylanhydrobartogenate (**6**). The mass spectrum of **6** showed an intense fragment at *m/z* 260 due to retro-Diels-Alder fission of ring-C indicating that the two acetoxyls and a carbomethoxyl group were present in rings-A and -B, respectively while rings D and E each had a carbomethoxyl group. The compounds (**6**) and (**21**) showed UV absorption at $_{max}$242 nm (ε, 7900) indicating the presence of a heteroannular diene.

The PMR spectrum of **6** indicated the presence of two acetoxyls at δ 1.98 and 2.08 as singlets, two protons geminal to acetoxyls at 4.84 (*d*, *J* = 10 Hz) and 5.70 (*m*); two vinyl protons at δ 5.40 and 5.48 besides the methoxyl, methyl and methylene resonances. From the coupling of the protons geminal to the acetoxyls it is clear that their orientation is *trans* diaxial. Hence the acetoxyls are present in *trans*-diequatorial configuration as in the case of dimethyl diacetyl bartogenate (**3**). The presence of 12,18-diene system is inferred from the PMR spectrum of **6** since the protons of the isomeric 11,13(18) show an *ABX* pattern, the 12-H being deshielded appeared at δ 6.5 as in the spectra of **7**, **12**, **13**, **16** and **17**. The signal for 19-H appeared as a singlet at 5.4 while the 12-H appeared as a triplet at 5.48. Further confirmation of the presence of 12,18-diene system was obtained by the isomerisation of **6** with MeOH-HCl into the known and stable transoid diene (**7**) having the typical UV absorption spectrum. This conclusively established the structure of anhydrobartogenic acid as 2α,3β-dihydroxyolean-12,18-diene-24,28-dioic acid (**20**).



(20) R = R$_1$=H
(21) R = Me ; R$_1$ =H
(6) R = Me ; R$_1$=Ac



(22) R= R$_1$= H
(23) R=Me ; R$_1$ =H
(24) R=Me ; R$_1$ =Ac

19-*Epi-Bartogenic acid* (**22**)

It analysed for $C_{30}H_{46}O_7$, m.p. 288-90°, $[\alpha]_D$ + 80° (Py), furnished a dimethyl ester (**23**), m.p. 252-54°, $[\alpha]_D$ + 100° ($CHCl_3$) and a diacetyl dimethyl ester (**24**), m.p. 138-48°. The IR spectrum of dimethyl diacetyl-19-epi-bartogenate showed the presence of a free hydroxyl, acetate and ester functions. Further acetylation with Ac_2O-$HClO_4$ yielded an amorphous acetate. The dimethyl ester (**23**) consumed nearly one mol of periodic acid indicating an α-glycol system.

The mass spectra of **23** and **24** were characterised by an intense peak at *m/z* 278 due to retro-Diels-Alder fission of ring-C indicating that the two hydroxyl and a carbomethoxyl groups are present in rings-A and B, respectively while the third hydroxyl and the carbomethoxyl groups are present in rings D and E, respectively. Further the fragmentation patterns were similar to those of dimethyl bartogenate (**2**) and its diacetate (**3**), respectively.

The ^{1}PMR spectrum of **24** showed the presence of two protons geminal to the acetoxyls in *trans*-diaxial system (δ 4.85, *d*, *J* = 10 Hz; 5.69, *m*). A β-axial carbomethoxyl group at C-4 deshielded the 2β-proton as observed in **3** and **6**.

Oxidation of **24** with CrO_3-pyridine furnished a ketone, m.p. 236-38°, which was identical with **4** obtained by the oxidation of **3**. The ketone from **24** isomerised readily to an α,β,δ-unsaturated ketone (**5**). Thus the new acid is an epimer of bartogenic acid,

having the 19-hydroxyl group in β-equatorial configuration. This is supported by the PMR spectrum of **22** wherein the 19α-axial proton appeared as a doublet at δ 3.36 (J = 11 Hz) by coupling with the 18β-H (2.58, *d*, J = 11 Hz), which are in a *trans* diaxial relationship. Thus the structure of 19-epi-bartogenic acid is established as 2α,3β,19β-trihydroxyolean-12-en-24,28-dioic acid (**22**).

Mass spectra

The fragmentation patterns of dimethyl diacetyl-bartogenate (**3**) and dimethyl diacetyl-19-*epi*-bartogenate (**24**), determined from similar accurate mass measurements of the ions, are similar and differ only in the intensity of the peaks (Chart 1).

The molecular ion (*A*) appeared at *m/z* 630 (40%) which is fragmented to the ions (*B*) and (*C*) at *m/z* 278 (100%) and 352 (14%) respectively due to the facile retro-Diels-Alder reaction of ring-C. This is confirmed by the presence of a metastable peak at *m/z* 122.5. Ion (*A*) loses 18 mass units resulting in the ion (*D*) at *m/z* 260 (70%) which further loses 59 mass units giving finally the ion (*E*) at *m/z* 201 (95%). Loss of 59 mass units from the ion (*B*) yields the ion (*F*) at *m/z* 219 (24%) which yields the ions (*G*) and (*H*) *m/z* 206 (10%) and 188 (40%), respectively. Ion (*F*) loses 76 mass units affording the ion (*I*) at *m/z* 133 (40%).

The ion (*C*) loses successively 60, 60 and 59 mass units giving the ions (*J*), (*K*) and (*L*) at *m/z* 292 (14%), 232 (15%) and 173 (44%) respectively.

The molecular ion *A* is fragmented into the ions (*M*), (*N*) and (*O*) due to the facile loss of 18, 60 and 60 mass units respectively.

CMR spectra

Tori *et al.*[16] have investigated the ^{13}C NMR spectra of several pentacyclic triterpenes and the signal assignments which were based on known chemical rules have been used for structural studies.

The CMR spectra of dimethyl bartogenate (**2**), methyl sericiate, methyl arjunolate and methyl oleanolate have been recorded and the assignments are indicated in Table 1. Some salient features are noted below.

Comparison among the carbons bearing hydroxyl substituents is found to be of diagnostic value. Thus the C-2 in dimethyl bartonate, methyl sericiate and methyl arjunolate appeared at δ 69-70 as doublets, whereas in methyl oleonolate C-2 appeared as a triplet at 27.3. The peaks appearing as doublets at δ 81.9 and 82.2 in methyl bartogenate and methyl sericiate, respectively are attributed to the C-19 since they were absent in oleanolate and arjunolate.

The vinylic carbons appear at the same position in all these compounds. Thus the C-12 carbons appeared in the range δ 122-125 as doublets while the C-13 carbons appeared as singlets at 143-144.

The signal due to the C-4 carbon appeared as a singlet at δ 38.8 in methyl oleanolate. However replacement of the methyl substituent at C-4 by a

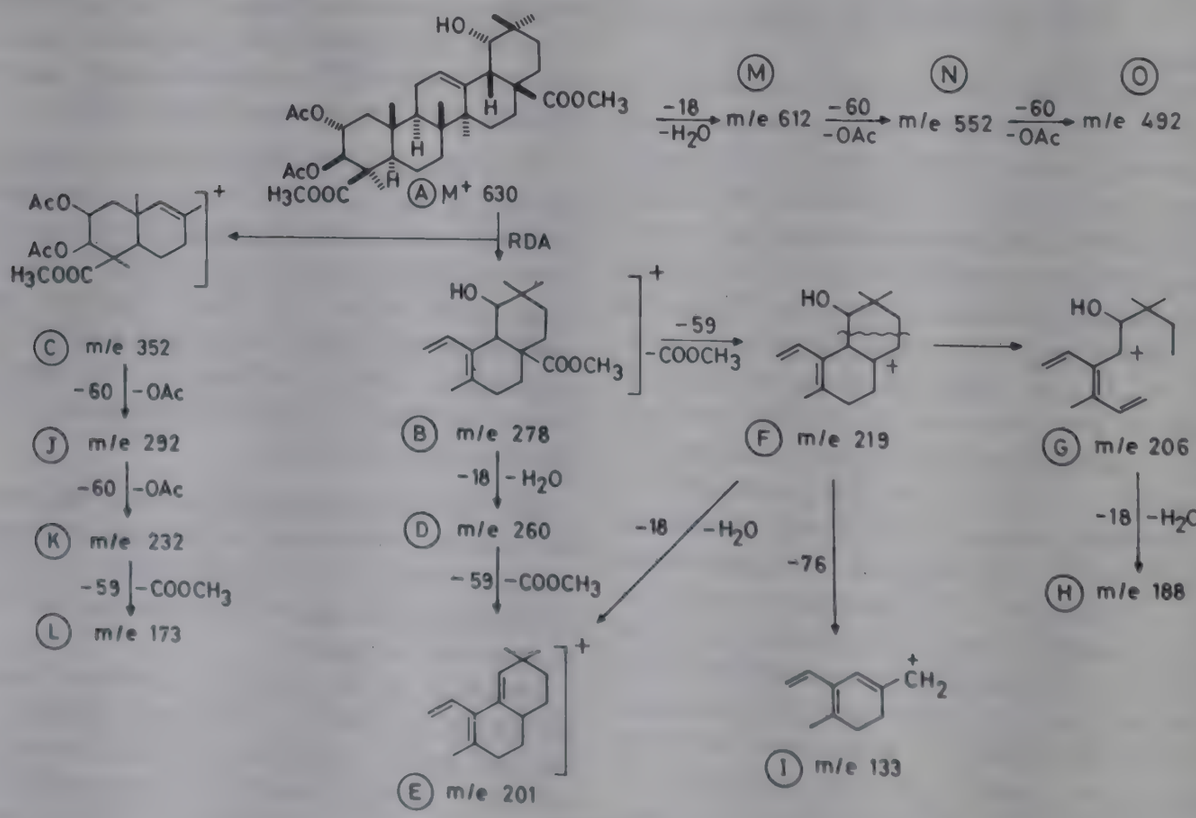


CHART 1

Table 1—Carbon-13 NMR Data of Various Methyl Esters

Carbon assigned	Dimethyl bartogenate	Methyl sericiate	Methyl arjunolate	Methyl oleanolate*
1	38.4	38.4	38.3	38.6(38.5)
2	69.8	69.1	69.7	27.3(27.1)
3	80.9	81.9	80.1	79.1(78.7)
4	58.5	48.9	48.1	38.8(38.7)
5	56.3	56.2	58.3	55.4(55.2)
6	18.4	18.4	18.4	18.4(18.3)
7	32.6	32.6	32.7	32.8(32.6)
8	39.3	39.8	39.5	39.4(39.3)
9	47.7	48.1	47.7	47.8(47.6)
10	37.5	38.0	38.2	37.1(37.0)
11	23.8	23.1	23.2	23.2(23.1)
12	124.6	124.7	122.3	122.4(122.1)
13	143.7	143.1	144.0	143.8(143.4)
14	42.0	41.8	41.9	41.8(41.6)
15	27.7	27.7	27.8	27.8(27.7)
16	23.5	23.5	23.5	23.5(23.4)
17	46.7	46.2	46.9	46.8(46.6)
18	41.5	41.5	41.5	41.5(41.3)
19	81.9	82.2	46.03	46.0(45.8)
20	28.2	28.3	30.7	30.7(30.6)
21	34.0	34.8	34.03	33.9(33.8)
22	32.7	32.9	32.5	32.4(32.3)
23	28.3	28.1	69.8	28.2(28.1)
24	185.2	65.6	28.2	15.6(15.6)
25	14.2	16.9	12.9	15.4(15.3)
26	16.7	17.05	17.08	16.9(19.8)
27	24.8	25.0	26.1	26.0(26.0)
28	178.5	178.6	178.3	178.3(178.3)
29	32.9	32.9	33.1	33.1(33.1)
30	51.3	23.6	23.6	23.6(23.6)
$COOCH_3$	51.7	51.7	51.7	51.5(51.5)

*Values given in brackets are the reported values as in [6].

hydroxymethyl or a carboxymethyl group considerably deshielded the C-4 carbon, appearing at δ 48-50 and 58.46 (Table 1).

The C-23 and C-24 carbons, bearing hydroxyl substituents in methyl arjunolate and methyl sericiate appeared as triplets at δ, 69.8 and 65.6 respectively. The corresponding C-23 and C-24 methyl groups of methyl oleanolate appeared at δ 28.0. The C-28 carbonyl carbon of the ester group appeared at δ 178 in all these compounds. However the C-24 carbonyl carbon of dimethyl bartogenate is very much deshielded and appeared at δ 185.2. This observation is noteworthy since this can be of diagnostic utility in determining the absolute stereochemistry at C-4 centre. The CMR spectrum of dimethyl 19-epi-bartogenate is very similar to dimethyl bartogenate.

Experimental Procedure

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer model-700 or Perkin-Elmer model-297 in nujol mull, unless otherwise stated, the UV spectra in ethanol on a Shimadzu model UV-180 and mass spectra recorded on a JEOL DX-300 instrument. ^1H NMR spectra were recorded on a Varian HA-100 D or Varian T-60 or Brucker WH-270 MHz spectrometer, using tetramethylsilane as an internal reference and chemical shift values are given in δ-scale (ppm). ^{13}C NMR were recorded on a Brucker 270 MHz spectrometer. Thin layer chromatography tests (TLC) and separations were carried out on glass plates coated with silica gel and the spots rendered visible by brief exposure to iodine vapour. Hexane refers to the petrol fraction, b.p. 60-80°.

Extraction of B. speciosa

Dried, powdered berries of *B. speciosa* (2 kg) were defatted with hexane and successively extracted with chloroform and methanol for 24 hr in a soxhlet set-up. The chloroform extract (2 litres) was concentrated to 500 ml and separated into acidic and neutral parts by shaking with a saturated aq. sodium bicarbonate. The aqueous part on acidification with dil. hydrochloric acid (1:1) under ice cooling gave a gelatinous precipitate, which was filtered, washed well with distilled water and dried (1 g). TLC (chloroform-ethyl acetate, 3:1) pattern of the acidic part showed it to be a mixture of two components. The acidic portion was esterified with ethereal diazomethane, and separated by preparative TLC (chloroform-ethyl acetate, 4:1) into the major (700 mg; R_f 0.45) and the minor (120 mg; R_f 0.40) components. Hydrolysis of the major ester with aq. potassium hydroxide in dimethyl sulphoxide at 60° for 12 hr afforded bartogenic acid (**1**) which recrystallised from acetone as small prisms, m.p. 317-18°. The minor ester was separated by preparative TLC into dimethylanhydrobartogenate (**21**) and dimethyl 19-epibartogenate (**23**).

The methanol extract (2 litres) was concentrated to a small volume (400 ml) and diluted with water (700 ml). The dark brown mixture was heated for 2 hr on a steam-bath with 8% sulphuric acid, cooled and the precipitated solid washed with water and dried (5 g). The solid thus obtained was digested with ether (3 × 500 ml), left overnight and filtered. The ethereal solution was separated into acidic and neutral parts by extracting it with a saturated aq. sodium bicarbonate (3 × 400 ml), the aqueous layer separated, neutralised with dil. hydrochloric acid, filtered, washed with water and dried (3 g). The neutral part (1.5 g) was a complex mixture and showed the presence of several compounds and its examination was deferred.

A methanolic solution of the acidic part from the methanol extract was treated with ethereal diazomethane under ice cooling and left for 1 hr. Excess of diazomethane was destroyed with glacial acetic acid and the solvent was removed completely to give a

yellow crystalline mass. TLC of this mixture (ethyl acetate-chloroform, 1:4) showed two distinct spots with R_f values 0.45 and 0.40. The major portion of the mixture was found to be dimethyl ester (**2**) of bartogenic acid (**1**), as described.

The mixture was separated by preparative TLC (chloroform:ethyl acetate, 4:1). The less polar fractions were combined and crystallised from hexane-methanol to give (**2**) as fine needles (2 g), m.p. 275-78°, $[\alpha]_D^{32}$ = 113.6 ($CHCl_3$): UV: 206 nm; IR: 3650, 1720 cm^{-1}; PMR: 0.69 (*s*, 3H), 0.80 (*s*, 3H), 0.99 (*s*, 6H), 1.28 (*s*, 3H), 1.41 (*s*, 3H) (*t*-methyls), 2.88 (*d*, 1H, 3α-H, *J* = 10 Hz), 3.15 (*bs*, 1H, 18 βH), 3.3 (*d*, 1H, 19β-H, *J* = 6 Hz), 4.01 (*sextet*, 1H, 2β-H), 5.43 (*t*, 1H, 12-H), 3.63 (*s*, 3H, $-COOCH_3$), 3.71 (*s*, 3H, $-COOCH_3$); MS: *m/z* 546 (M^+, 30), 278 (100), 260 (93), 201 (95). (Found: C, 70.81; H, 9.07. $C_{32}H_{50}O_7$ requires C, 70.3; H, 9.1%). Hydrolysis of **2** with potassium hydroxide in dimethyl sulphoxide as above and followed by usual work-up afforded bartogenic acid (**1**), m.p. and m.m.p. 317-18°.

Dimethyl-12,13-*epoxybartogenate*

A solution of **2** (80 mg) in dry chloroform (20 ml) was cooled to 0°C and *m*-chloroperbenzoic acid (50 mg) added with stirring. The reaction mixture was kept at 0-10° for 48 hr, diluted with chloroform (150 ml) and washed with 5% aq. sodium hydroxide (3 × 20 ml) to neutralise the excess of acid. The chloroform solution was washed with brine and water, dried, solvent evaporated and the residue crystallised from methanol to afford the epoxy compound as flakes (34 mg), m.p. 182-85° (Found: C, 67.8; H, 9.2. $C_{32}H_{50}O_8$ requires C, 68.32; H, 8.9%).

Acetylation of **2**

A mixture containing **2** (300 mg), dry acetic anhydride (2 ml) and pyridine (1 ml) was heated on a steam-bath with occasional stirring for 2 hr under anhydrous conditions. After 8 hr, the reaction mixture was poured over crushed ice and the crude acetate filtered, washed with water and dried. The TLC (hexane-ethyl acetate, 85:15) showed it to be a mixture of two components. The mixture was separated by preparative TLC into the diacetate (**3**) and the monoacetate.

The diacetate (100 mg) crystallised from hexane-methanol, m.p. 195-96°, $[\alpha]_D^{33}$ = 21.51°; UV: 206, 284 nm; IR: 3650, 1730, 1720 cm^{-1}; PMR: 0.69 (*s*, 3H), 0.80 (*s*, 3H), 0.99 (*s*, 6H), 1.28 (*s*, 6H) (tertiary methyls), 1.99 (*s*, 3H, CH_3CO), 2.01 (*s*, 3H, CH_3CO), 3.15 (*bs*, 1H, 18β-H), 3.3 (*d*, 1H, 19β-H), 3.63 (*s*, 3H, 28-$COOCH_3$), 3.71 (*s*, 3H, 24-$COOCH_3$), 4.85 (*d*, 3H, 3α-H, *J* = 10 Hz), 5.43 (*bt*, 1H, vinylic 12-H), 5.72 (*sextet*, 1H, 2H); MS: *m/z* 630 (M^+ 40), 612 (20), 552 (29), 492 (20), 352 (14), 292 (14), 278 (100), 260 (70), 232 (15), 219 (24), 206 (11), 201 (95), 188 (40), 173 (44), 133 (40). (Found: C, 67.9; H, 8.7. $C_{36}H_{54}O_9$ requires C, 68.5; H, 8.6%).

The monoacetate crystallised from hexane-methanol as prisms (60 mg), m.p. 156-58°; UV: 206, 284 nm; IR: 3650, 1730, 1720 cm^{-1}; PMR: 0.69 (*s*, 3H), 0.80 (*s*, 3H), 0.99 (*s*, 6H), 1.28 (*s*, 3H), 1.41 (*s*, 3H) (*t*-methyls), 1.99 (*s*, 3H, CH_3CO), 2.88 (*d*, 1H, 3α-H), 3.15 (*bs*, 1H, 18β-H); 3.3 (*d*, 1H, 19β-H), 3.63 (*s*, 3H, 28-$COOCH_3$), 3.71 (*s*, 3H, 24-$COOCH_3$), 5.43 (*bt*, 1H, vinylic, 12-H), 5.45 (*m*, 1H, 2β-H). (Found: C, 69.4; H, 9.0; $C_{34}H_{52}O_8$ requires C, 69.4; H, 8.9%).

Compound (**3**, 50 mg) in acetic anhydride (1 ml) was treated with perchloric acid (two drops) at 0°. The triacetate was obtained as an amorphous powder (25 mg), which resisted crystallisation; IR: 1740, 1720 cm^{-1}.

Chromium trioxide oxidation of Dimethyl 2α,3β-*diacetyl*-19α-*hydroxybartogenate* (**3**): *Dimethyl* 2α,3β-*diacetyl*-19-*keto-bartogenate* (**4**)

3 (100 mg) in dry acetone (40 ml), was treated with chromium trioxide solution (prepared by dissolving 1 g of chromium trioxide in 10 ml of water and 1 ml of conc. sulphuric acid) under vigorous swirling. A dark green precipitate separated out, which progressively increased in quantity. After the addition was complete, the mixture was kept at room temperature for 20 min with occasional swirling. Water was added to the reaction mixture, warmed on a water-bath, filtered, washed and dried. The crude product was crystallised from methanol to give pure **4** (78 mg), m.p. 236-38°; $[\alpha]_D^{22}$ −63.31°; UV: 292 nm (ε, 90); IR: 1730, 1710 cm^{-1}. (Found: C, 68.4; H, 8.4. $C_{36}H_{52}O_9$ requires C, 68.8; H, 8.3%).

Dimethyl 2α,3β-*diacetyl*-19-*keto-olean*-13(18)-*ene*-24,28-*dioate* (**5**)

4 (20 mg) was refluxed with methanolic potassium hydroxide (2 drops of 5% solution) for 30 min on a steam-bath. Excess of solvent was evaporated under reduced pressure, extracted with ether, the ethereal solution dried and the solvent removed to give a solid which was acetylated (Ac_2O, Py) and worked-up in the usual manner to give the crude acetate. This was crystallised from methanol to afford **5** (12 mg), m.p. 224-26°; UV: 253 nm (ε, 7100); IR: 1730, 1720 and 1690 cm^{-1} (Found: C, 68.6; H, 8.3. $C_{36}H_{52}O_9$ requires C, 68.8; H, 8.3%).

Wolf-Kishner reduction of **4**

Sodium (0.15 g) in diethyleneglycol (8 ml) was heated to 180° and anhydrous hydrazine (3 ml) added until the mixture started refluxing. To this was added **4** (60 mg) rapidly, the mixture refluxed at 210° for 24 hr, poured

into water and the precipitate collected (45 mg). The precipitate thus obtained was subjected to acetylation with acetic anhydride (1 ml) and pyridine (0.5 ml) and worked-up in the usual manner. The crude acetate was crystallised from methanol (25 mg), m.p. 131°; IR: 1720, 1730 cm^{-1} (Found: C, 69.8; H, 9.0. $C_{36}H_{56}O_8$ requires C, 70.1; H, 9.1%).

Formation of dimethyl 2α,3β-*diacetylolean*-11,13(18)-*diene*-24,28-*dioate* (**7**): SeO_2 *oxidation of* **3** (*method-I*)

Compound (**3**, 100 mg) in acetic acid (10 ml) was heated to boiling with selenium dioxide (50 mg). The deposition of black metallic selenium started very quickly. The reaction mixture was allowed to reflux for 4 hr, cooled, filtered and the filtrate diluted with water (100 ml). The precipitate thus obtained was dried and crystallised from methanol to afford **7** as an amorphous powder (50 mg), m.p. 141-44°.

Method-II

3 (200 mg) in dry pyridine (3 ml) was treated dropwise with phosphorus oxychloride (1.5 ml). The solution was kept at room temperature for 8 hr, poured onto crushed ice, extracted with ether, washed thoroughly free of acids and dried. Removal of the solvent gave a yellow mass which was chromatographed on neutral alumina. Elution with hexane-benzene (4:1) followed by crystallisation from hexane-methanol gave the diene (**6**) as needles.

The above diene mixture (150 mg) was dissolved in dry chloroform (20 ml) and a stream of dry hydrogen chloride was passed for 4 hr and left overnight. The solvent was removed under reduced pressure, the residue diluted with water, extracted with ether and dried. Removal of the solvent afforded a semi-solid (120 mg), which was acetylated with acetic anhydride (1 ml) in pyridine (2 ml) and worked-up in the usual manner to give the crude diene (**7**), which was purified by preparative TLC (hexane-ethyl acetate = 85:15). The product was crystallised from benzene-hexane (120 mg), m.p. 141-44°; UV: 244, 252, 261 nm (ε, 19950, 25120, 16600); IR: 1730, 1720 cm^{-1}; PMR: 0.65 (3H), 0.75 (3H), 0.98 (6H), 1.04 (6H, *t*-methyls), 1.98 (*s*, 3H, $COCH_3$), 4.85 (*s*, 3H, $COCH_3$), 3.65 (*s*, 3H, $COOCH_3$), 3.71 (*s*, 3H, $COOCH_3$), 4.85 (*d*, 1H, 3α-H, $J = 9.9$ Hz), 5.58 (*d*, 1H, 12-H, $J = 10.8$ Hz), 5.72 (*m*, 1H, 2β-H), 6.4 (*d* of *d*, 1H, 11-H) (Found: C, 70.0; H, 8.5. $C_{36}H_{54}O_8$ requires C, 70.4; H, 8.8%). It was found to be identical with **7** obtained by method-I.

Methyl sericiate (**8**)

3 (200 mg) in dry benzene (50 ml) was treated with a slight excess of vitride reagent (sodium bis[2-methoxyethoxy]aluminiumhydride 70% solution in benzene), refluxed on a steam-bath for 4 hr, cooled and diluted with benzene. The benzene layer was washed with saturated solution of Rochelle's salt, the organic layer separated and the aqueous layer extracted with ether (3 × 50 ml). The combined organic layer was dried and the solvent removed to give a gum (140 mg) which crystallised from methanol to give pure **8** (80 mg); m.p. 162° (lit.[12] m.p. 160-63°), $[\alpha]_D^{32}$ 39.5° (identical with authentic sample) (Found: C, 71.7; H, 9.7. Calc. for $C_{31}H_{50}O_6$: C, 71.8; H, 9.7%).

Methyl sericiate (100 mg) was acetylated Ac_2O (2 ml)/Py (1 ml) by heating the mixture over a steam-bath with occasional swirling for 2 hr. The reaction mixture was kept at room temperature for 8 hr, poured onto crushed ice and the solid obtained filtered, dried, and crystallised from methanol to give fine crystals of methyl 2α,3β,24-triacetyl-19α-hydroxy-olean-12-ene-28-oate (**9**; 70 mg), m.p. 178°; $[\alpha]_D^{32} = -10°$; UV: 206, 283; IR: 3650, 1740 cm^{-1}; PMR: 0.69 (3H), 0.99 (6H), 1.08 (3H), 1.10 (3H), 1.25 (3H, *t*-methyls); 2.0 (*s*, 3H, $COCH_3$), 2.08 (*s*, 6H, $COCH_3$), 3.16 (*bs*, 1H, 18β-H), 3.34 (*bs*, 1H, 19β-H), 3.63 (*s*, 3H, $COOCH_3$), 4.18 (*s*, 2H, C-24 CH_2), 4.75 (*d*, 1H, 3-H, $J = 10$ Hz), 5.16 (*sextet*, 1H, 2β-H), 5.43 (*bt*, 1H, vinylic H) (Found: C, 68.9; H, 8.8; $C_{37}H_{56}O_9$ requires C, 68.9; H, 8.8%).

2α,3β,24,28-*Tetraacetyl*-19α-*hydroxy*-*olean*-12-*ene* (**16**)

To a suspension of lithium aluminium hydride (250 mg) in dry THF (60 ml) was added dropwise a solution of **3** (150 mg) in dry THF (30 ml) over a period of 30 min. The reaction mixture was refluxed on a steam-bath for 6 hr, cooled, the excess of the lithium aluminium hydride decomposed by the addition of ethyl acetate and diluted with water. The mixture was extracted with ether, washed with water and dried. Removal of the solvent gave a gummy mass (110 mg) which resisted crystallisation (ν_{max} 3650 cm^{-1}). Acetylation of this gum was carried out with acetic anhydride (2 ml) and pyridine (1 ml). The mixture was heated in a steam-bath for 2 hr, kept at room temperature for 8 hr, poured onto crushed ice, warmed and filtered. The precipitate was washed well, dried and crystallised from methanol to give pure **16** (180 mg), m.p. 122-23°; IR: 1730, 1720 cm^{-1}; PMR: 0.69 (3H), 0.80 (3H), 0.99 (6H), 1.28 (6H) (*t*-methyls); 1.99 (*s*, 3H, $COCH_3$), 2.01 (*s*, 6H, two $COCH_3$), 3.15 (*d*, 1H, 18-β-H), 3.3 (*d*, 1H, 19β-H); 3.85 (*m*, 2H, 28-CH_2OAc), 4.18 (*s*, 2H, 24-CH_2OAc), 4.75 (*d*, 1H, 3α-H), 5.16 (*s*, 1H, 2β-H), 5.4 (*bt*, 1H, vinylic H). (Found: C, 69.1; H, 8.9. $C_{38}H_{58}O_9$ requires C, 69.3; H, 8.5%).

2α,3β,24,28-*Tetraacetylolean*-11,13(18)-*diene* (**17**)

The tetraacetate (**16**, 80 mg) in dry pyridine (2 ml)

was treated with phosphorus oxychloride (1 ml) under cooling and left overnight at room temperature. The reaction mixture was poured onto crushed ice, extracted with ether, the ethereal solution washed with dilute acid, water and dried. Removal of the solvent gave a gummy residue which was isomerised as follows.

A stream of dry hydrogen chloride gas was passed through a solution of the crude dehydrated compound (60 mg) in dry chloroform (10 ml) for 4 hr and the mixture kept overnight. This was diluted with chloroform and the chloroform layer washed with water and dried. Removal of the solvent under reduced pressure afforded a gum which was acetylated with acetic anhydride in pyridine and worked-up in the usual way to give a crude product which was crystallised from methanol to afford **17** (3 mg), m.p. 129 ; $[\alpha]_D^{22} = -65.2$; UV: 244, 251, 262 nm (ε, 19950, 25120, 16600); IR: 1730 cm^{-1}; PMR: 0.65 (3H), 0.75 (3H), 0.98 (6H), 1.04 (6H) (*t*-methyls); 1.96 (*s*, 3H, $-COCH_3$), 2.05 (*s*, 6H, two $-COCH_3$), 4.06 (*q*, 2H, 28-CH_2OAc, $J=11$ Hz), 4.18 (*s*, 2H, 24-CH_2OAc), 4.85 (*d*, 1H, 3α-H, $J=9.9$ Hz), 5.2 (*m*, 1H, 2β-H), 5.58 (*d*, 1H, 12-H, $J=10.8$ Hz), 6.4 (*d* of *d*, 1H, 11-H). (Found: C, 70.9; H, 9.3. $C_{38}H_{56}O_8$ requires C, 71.2; H, 8.8%).

Methyl arjunolate (**10**)

Arjunolic acid (500 mg) was suspended in methanol (15 ml) and treated with excess of ethereal diazomethane. Usual work-up afforded a pale yellow crystalline mass which was purified by crystallisation from ether-methanol to give **10** (470 mg), m.p. 209.5° (lit.[6] m.p. 209-11°; $[\alpha]_D^{31} = 68°$; UV: 206, 282 nm; IR: 3650, 1720 cm^{-1}; PMR: 0.69 (3H), 0.85 (3H), 0.90 (3H), 0.95 (3H), 0.99 (3H), 1.15 (3H) (*t*-methyls); 2.88 (*d*, 1H, 3α-H, $J=10$ Hz), 3.4 (*bm*, 2H, CH_2OH), 3.75 (*m*, 1H, 2β-H), 5.28 (*m*, 1H, vinylic H). (Found: C, 73.9; H, 10.3. Calc. for $C_{31}H_{50}O_5$; C, 74.1; H, 10.0%).

Methyl arjunolate (500 mg) was acetylated with a mixture of acetic anhydride (5 ml) and pyridine (2.5 ml) by heating on a steam bath for 2 hr, cooled to the room temperature, the reaction mixture poured onto crushed ice, the solid that separated out was filtered, washed well with distilled water, dried and crystallised from methanol to give methyl 2α,3β,23-triacetyl-arjunolate (**11**, 350 mg), m.p. 268-69° (lit.[6] m.p. 268-70°); IR: 1730, 1720 cm^{-1}; PMR: 0.79 (3H), 0.85 (3H), 0.98 (6H), 1.18 (6H) (*t*-methyls); 1.98 (*s*, 3H, CH_3CO), 2.00 (*s*, 3H, CHCO), 2.01 (*s*, 3H, CH_3CO), 3.65 (*s*, 3H, $COOCH_3$), 3.55 (*q*, 2H, CH_2OAc), 5.15 (*m*, 2H, 3β-H and 2α-H), 5.4 (*m*, 1H, vinylic H). (Found: C, 74.5; H, 7.9. Calc. for $C_{37}H_{56}O_8$; C, 74.6; H, 7.9%).

Methyl anhydroarjunolate (**13**)

Compound (**11**, 300 mg) in glacial acetic acid (20 ml) was heated to boiling with selenium dioxide (100 mg) for 18 hr, cooled, filtered and the filtrate diluted with water (100 ml). The precipitate thus obtained was dried and crystallised from methanol as an amorphous powder (105 mg), m.p. 250-51° $[\alpha]_D^{23} = -52°$; UV: 242, 251, 262 (ε, 20000, 25000, 16000); IR: 1730, 1720 cm^{-1}; PMR: 3.65 (*s*, 1H, $COOCH_3$), 3.65 (*q*, 2H, 23-CH_2OAc), 4.85 (*d*, 1H, 3α-H, $J=10$ Hz), 5.01 (*m*, 1H, 2β-H), 5.56 (*d*, 1H, 12-H, $J=10$ Hz), 6.64 (*d* of *d*, 1H, 11-H) (Found: C, 70.5; H, 8.7. $C_{30}H_{54}O_8$ requires C, 70.7; H, 8.9%).

2α,3β,23,28-*Tetraacetylolean*-11,13(18)-*diene* (**18**)

13 (80 mg) in dry THF (10 ml) was added to a suspension of lithium aluminium hydride (50 mg) in dry THF (10 ml). The mixture was refluxed for 6 hr, cooled and worked-up to give a tetrahydroxy compound which resisted crystallization. This compound was mixed with acetic anhydride and pyridine and heated on a steam-bath for 2 hr. The mixture was kept at room temperature for 8 hr, poured onto crushed ice, the pale yellow solid collected and crystallised from methanol to give **18** (48 mg), m.p. 196° (lit.[4] m.p. 196-97°); $[\alpha]_D = -72°$; UV: 244, 251, 262 nm (ε, 19900, 25120, 16600); IR: 1730 cm^{-1}; PMR: 3.55 (*m*, 2H, 28-CH_2OAc), 3.65 (*q*, 2H, 23-CH_2OAc, $J=11$ Hz), 5.05 (*d*, 1H, 3α-H), 5.2 (*m*, 1H, 2β-H), 5.51 (*d*, 1H, 12-H, $J=11$H), 6.7 (*d* of *d*, 1H, 11-H) (Found: C, 71.8; H, 8.8. Calc. for $C_{38}H_{56}O_8$: C, 71.1; H, 8.8%).

Methyl 2α,3β,24-*triacetoxyolean*-11,13(18)-*dien*-28-*oate* (**12**)

Compound (**9**, 100 mg) in dry pyridine (2 ml) was treated with phosphorus oxychloride (1.5 ml) under cooling, left overnight at room temperature, poured onto crushed ice, extracted with ether and the ethereal solution washed with dilute acid, water and dried. Removal of solvent gave the dehydrated product (50 mg) which was isomerised as follows.

A stream of dry hydrogen chloride gas was passed through a solution of the crude dehydrated product (50 mg) in dry chloroform (10 ml) for 4 hr and the mixture kept overnight. The reaction mixture was diluted with chloroform and the chloroform worked-up to yield a gummy solid. This gum was acetylated with acetic anhydride in pyridine and the diene (**12**) was crystallised from methanol, m.p. 144°; UV: 244, 252, 261 nm (ε, 19050, 25000, 16000); IR: 1730 cm^{-1} (Found: C, 70.5; H, 8.7. $C_{37}H_{54}O_8$ requires C, 70.7; H, 8.9%).

Methyl 2α,3β,24-*tribenzoyloxyolean*-11,13(18)-*dien*-28-*oate*

The above diene (**12**, 25 mg) was refluxed with methanolic potassium hydroxide (5% solution, 5 ml)

for 2 hr on a water-bath. The excess of methanol was removed under reduced pressure, the solid obtained filtered, washed with water and dried. To a solution of the above residue in pyridine (1 ml) was added two drops of benzoyl chloride, keeping the temperature at −5°. The mixture was kept at room temperature overnight, diluted with water and extracted with ether to give the tribenzoate which was crystallised from ethanol (25 mg), m.p. 173°; UV: 230, 244, 252, 261 nm (ε, 30000, 20000, 25000, 17000); IR: 1720, 1600, 1585 cm^{-1}; CD maxima Δ, +7.2. (Found: C, 80.1; H, 7.7. $C_{52}H_{60}O_8$ requires C, 80.0; H, 7.7%).

Methyl 2α,3β,23-*tribenzoyloxyolean*-11,13(18)*dien*-28-*oate*

The diene (**13**, 20 mg) was refluxed with 5% solution of methanolic potassium hydroxide for 2 hr on a water-bath. Excess of methanol was removed under reduced pressure, the residue diluted with water, the precipitate obtained filtered off washed with and dried. The hydroxydiene thus obtained was dissolved in pyridine (1 ml) and cooled to −5°. To the cooled solution was added two drops of benzoyl chloride, left at room temperature for 24 hr and diluted with water. Extraction with ether afforded a crystalline solid, further recrystallised from ethanol (20 mg), m.p. 195-98°; UV: 230, 244, 251, 260 nm (ε, 32000, 19000, 25000, 17000); IR: 1720, 1600, 1585 cm^{-1}; CD maxima Δ −6.8. (Found: C, 79.9; H, 7.6. $C_{52}H_{60}O_8$ requires C, 80.0; H, 7.7%).

Methyl 2α,3β,24-*triacetylolean*-12-*en*-28-*oate* (**15**)

9 (50 mg) in dry pyridine (5 ml) was added to pyridine-chromium trioxide reagent (3 ml of pyridine containing 0.2 g of chromium trioxide) at room temperature. After 2 hr, the precipitate was filtered and washed with pyridine. The combined pyridine solution was poured into water (50 ml), extracted with ether, the ethereal layer washed with dil. hydrochloric acid (1:1), neutralised and dried. Removal of the solvent gave an amorphous material which was crystallised from methanol to give pure **15** methyl-2α,3β,24-triacetyl-19-keto-olean-ene-28-oate (**14**; 25 mg), m.p. 200-201° (lit.[12] m.p. 200°); $[\alpha]_D^{26}$ = +32.5°; UV: 292 nm (ε, 110); IR: 1735, 1730, 1710 cm^{-1} (Found: C, 83.0; H, 10.2. Calc. for $C_{37}H_{54}O_9$: C, 83.1; H, 10.2%).

Sodium (0.2 g) in diethyleneglycol (10 ml) was heated to 180° and anhydrous hydrazine (4 ml) was added until the mixture refluxed at 180°. To this was added **14** (100 mg) in one lot and the solution refluxed for 12 hr. The temperature was raised to 210° by distilling some amount of hydrazine and the solution refluxed at this temperature for 24 hr. The reaction mixture was poured into water, the precipitate collected (80 mg) and subjected to acetylation with acetic anhydride (0.5 ml)/pyridine (0.5 ml) by heating over a steam-bath for 2 hr. Reaction mixture was kept aside for 8 hr and worked-up in the usual manner. The crude product which resisted crystallisation gave **15** as an amorphous powder (40 mg), m.p. 140°; IR: 1730, 1720 cm^{-1} (Found: C, 70.4; H, 9.0. $C_{36}H_{56}O_8$ requires C, 70.5; H, 9.2%).

Dimethyl anhydrobartogenate (**21**)

This was crystallised from hexane-methanol (4:1) as needles, m.p. 270-72°; UV: 242 nm; IR: 3500, 1725 cm^{-1}; PMR: 0.78, 0.85, 0.87, 0.95, 0.98 and 1.25 (*s*, 3H each, six tertiary methyls): 3.61 (*s*, 3H, $-COOCH_3$), 3.69 (*s*, 3H, $-COOCH_3$), 2.92 (*d*, *J* = 10 Hz, 3α-H), 4.07 (*m*, 2β-H), 5.40 (*s*, 19-H), 5.48 (*t*, 12-H); M^+ at *m/z* 528 (Found: C, 72.2; H, 9.1. $C_{32}H_{48}O_6$ requires C, 72.7 and H, 9.1%).

Dimethyl diacetylanhydrobartogenate (**6**)

21 was treated with acetic anhydride (2 ml) in pyridine (1 ml) and left overnight. The reaction mixture was worked up and the product crystallised from hexane-methanol (5:1) yielding colourless needles of **6**, m.p. 140-42°; $[\alpha]_D$ + 80° ($CHCl_3$); UV: 242 nm (ε, 7900); IR: 1740, 1720 cm^{-1}; PMR: 0.84, 0.92, 0.94, 1.06, 1.17 and 1.26 (all singlets, six tertiary methyls); 1.97 (*s*, 3H, $-OCOCH_3$), 2.09 (*s*, 3H, $-OCOCH_3$), 3.61 (*s*, 3H, $-COOCH_3$), 3.69 (*s*, 3H, $-COOCH_3$), 4.84 (*d*, *J* = 11 Hz, 3α-*H*), 5.35 (*s*, 19-*H*), 5.46 (*t*, 12-H), 5.7 (*m*, 2β-H); MS: *m/z* (%) 6.2 (29), 553 (24), 493 (10), 433 (12), 260 (21), 247 (98) and 201 (60). (Found: C, 69.9; H, 8.4. $C_{36}H_{52}O_8$ requires C, 70.6 and H, 8.5%).

Dimethyl 19-*epibartogenate* (**23**)

This was obtained as prisms from methanol, m.p. 252-54°; $[\alpha]_D^{22}$ + 110 ($CHCl_3$); UV: 205 nm; IR: 3500, 1725 cm^{-1}; PMR: 0.77, 0.82, 0.90, 1.06, 1.16 and 1.25 (*s*, 3H each, six methyls); 2.59 (*d*, 1H, *J* = 11 Hz, 18β-H), 3.36 (*d*, 1H, *J* = 11 Hz, 19α-H), 3.49 (*d*, 1H, *J* = 11 Hz, 3α-H), 3.63 (*s*, 3H, $COOCH_3$), 3.68 (*s*, 3H, $COOCH_3$), 4.0 (*m*, 1H, 2β-H), 5.45 (*t*, 1H, 12-H); MS: *m/z* (%), 528 (100), 278 (15), 260 (20), 201 (90). (Found: C, 70.8; H, 9.0. $C_{32}H_{50}O_7$ requires C, 70.3; H, 9.2%).

Dimethyl Diacetyl-19-*epibartogenate* (**24**)

23 (200 mg) was treated with excess of acetic anhydride (2 ml) in pyridine (1 ml). The mixture was heated on a steam bath for 2 hr and worked-up as usual. The product was crystallised from methanol to furnish pure **24**, m.p. 138-40°; IR: 3540, 1740, 1720 cm^{-1}; PMR: 0.74, 0.88, 0.90, 1.06, 1.15 and 1.26 (*s*, 6 × CH_3); 1.99 (*s*, 3H, $-OCOCH_3$), 2.08 (*s*, 3H, $OCOCH_3$), 2.5 (*d*, 1H. *J* = 11 Hz, 18β-H), 3.36 (*d*, 1H. *J* = 11H, 19α-H), 3.63 (*s*, 3H, $COOCH_3$), 3.69 (*s*, 3H,

$COOCH_3$), 4.85 (*d*, 1H, $J=11$ Hz, 3α-H), 5.42 (*t*, 1H, 12-H), 5.69 (*m*, 1H, 2β-H); MS: *m/z* (%) 630 (4), 612 (47), 570 (4), 553 (11), 278 (17), 260 (44), 219 (9) and 201 (100). (Found: C, 67.9; H, 8.7. $C_{36}H_{54}O_9$ requires C, 68.6 and H, 8.6%).

19-*Epibartogenic acid* (**22**)

23 was hydrolysed with aq. potassium hydroxide in DMSO at 60° for 24 hr. The mixture was diluted with water and acidified to yield a white precipitate which crystallised from acetone to **22** as prisms, m.p. 288-90°; $[\alpha]_D^{22°}+80°$ (pyridine); IR: 3500, 1715 cm^{-1}. (Found: C, 69.5; H, 9.2. $C_{30}H_{46}O_7$ requires C, 69.5; H, 8.9%).

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Structure of New Galactomannan from Seeds of *Acacia leucophloea* Willd.

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A homogeneous galactomannan composed of D-galactose and D-mannose in a molar ratio of 1:1.35 has been isolated from the defatted seeds of *Acacia leucophloea* Willd. Hydrolysis of fully methylated galactomannan results in the formation of 2,3,4,6-tetra-O-methyl-D-mannose, 2,3,4,6-tetra-O-methyl-D-galactose, 3,4,6-tri-O-methyl-D-mannose, 3,4,6-tri-O-methyl-D-galactose, 3,4-di-O-methyl-D-mannose and 3,4-di-O-methyl-D-galactose in a molar ratio of 1:2.12:4.12:2.08:1.92:1.24. The polysaccharide consumes 1.21 mol of sodium metaperiodate with the liberation of 0.24 mol of formic acid. Smith degradation of periodate-oxidized compound produces only glycerol. Graded acid hydrolysis results in the generation of three disaccharides, viz. 2-O-β-D-galactopyranosyl-D-mannose, 6-O-α-D-galactopyranosyl-D-mannose, 6-O-α-D-galactopyranosyl-D-galactose; a trisaccharide, O-β-D-galactopyranosyl-(1→2)-β-D-mannopyranosyl-(1→2)-D-mannose; and one tetrasaccharide, O-β-D-galactopyranosyl-(1→2)-β-D-mannopyranosyl-(1→2)-β-D-mannopyranosyl-(1→2)-D-galactose. The results indicate that the main chain of galactomannan is made up of (1→2)-glycosidic-linked sugar residues with substitution at O-6.

The seeds of *Acacia leucophloea* Willd.[1] (fam: Leguminoseae; sub-fam: Minnoseae) are located in pods and contain mucilage in high yield. A systematic chemical investigation of *A. leucophloea* seed polysaccharide has been undertaken and the results are discussed in the present paper.

The polysaccharide was isolated from the defatted seeds by extraction with water and purified by repeated precipitation with ethanol followed by copper complex formation with cupric acetate[2]. Homogeneity of the polysaccharide was tested by paper electrophoresis, which was carried out in borate buffers (*p*H 9.2) under a field strength of 1000 V for 5 hr. The polysaccharide migrated as a single spot ($\mu = 0.013 \times 10^{-5}$ cm^2, V^{-1} S^{-1}) and it was detected by spraying with sodium metaperiodate-benzidine-B. The pure polysaccharide, $[\alpha]_D^{28} + 22°$ (NaOH) was found to be free from starch, pentoses, nitrogen, sulphur, halogen, methoxyl and anhydrouronic acid. Complete acid hydrolysis of the polysaccharide with 2 *M* trifluoroacetic acid (TFA) revealed the presence of galactose and mannose, characterized by the usual methods. The separation of individual sugar from the neutral sugar mixture was also carried out by GLC of their alditol acetates[3]. Estimation of the individual sugars by periodate oxidation[4], phenol-sulphuric acid method[5] and by GLC indicated a molar ratio of galactose to mannose as 1:1.35.

The polysaccharide was fully methylated by the Haworth method[6] followed by Hakomori method[7]. The IR spectrum of fully methylated polysaccharide was devoid of absorption band for −OH groups. The methylated compound was hydrolyzed according to procedure of Croon *et al.*[8]. The alditol acetates of the resulting methylated sugars were identified and their relative molar proportion determined by GLC. The results are summarized in Table 1. The isolation of one mol of 2,3,4,6-tetra-O-methyl-D-mannose and two mol of 2,3,4,6-tetra-O-methyl-D-galactose indicated that these residues constituted the three end groups in the average repeating unit of the polysaccharide. Similarly, the isolation of 3,4,6-tri-O-methyl-D-mannose and 3,4,6-tri-O-methyl-D-galactose showed that these components originated from the D-mannose and D-galactose residues linked to other units through O-1 and O-2. Further D-mannose and D-galactose residues which gave rise to 3,4-di-O-methyl-D-mannose and 3,4-di-O-methyl-D-galactose were joined to monosaccharide units through O-1, O-2 and O-6.

The distribution of (1→2)- and (1→6)-linkages in the framework of *A. leucophloea* seed polysaccharide was also evident from the results of periodate oxidation. Upon oxidation with sodium metaperiodate the galactomannan consumed 1.21 mol of periodate per mol of hexose unit to furnish 0.24 mol of formic acid. As the average repeating unit consisted of 12 anhydrohexose residues, the above results could be interpreted in terms of 2.88 mol of formic acid with simultaneous consumption of 14.52 mol of periodate. The total consumption of periodate by the polysaccharide (repeating unit) would then be 15 mol with simultaneous liberation of 3 mol of formic acid. Further, periodate-oxidized product when degraded according to Smith's procedure[9], gave rise to glycerol only. The experimental results thus confirm the presence of (1→2)- and (1→6)-glycosidic linkages in the polysaccharide.

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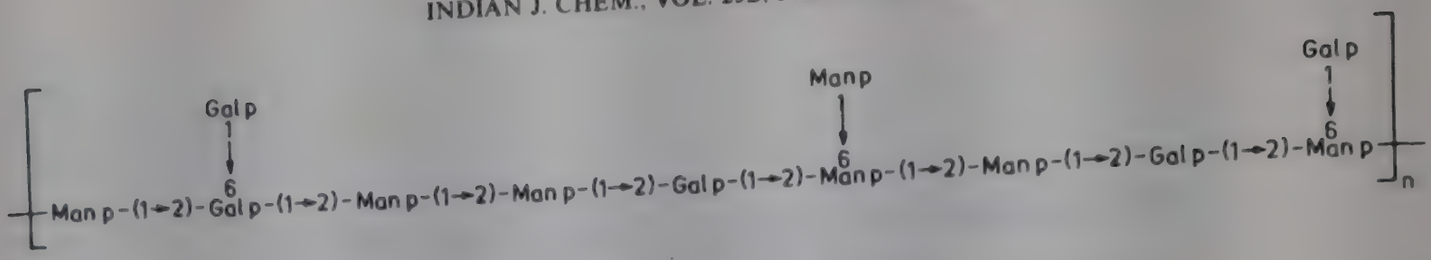

(I)

Graded hydrolysis of the galactomannan with 0.05 *M* sulphuric acid yielded D-galactose and D-mannose along with three disaccharides, a trisaccharide and a tetrasaccharide identified as 2-O-β-D-galactopyranosyl-D-mannose, 6-O-α-D-galacto-pyranosyl-D-mannose, 6-O-α-D-galacto pyranosyl-D-galactose, O-β-D-galacto pyranosyl-(1→2)-β-D-manno pyranosyl-(1→2)-D-mannose, and O-β-D-galactopyranosyl-(1→2)-β-D-manno pyranosyl-(1→2)-β-D-manno pyranosyl-(1→2)-D-galactose. The occurrence of 2-O-β-D-galactopyranosyl-D-mannose has not been reported in literature. However, its steroisomer 2-O-α-D-galacto pyranosyl-D-mannose, $[\alpha]_D$ +81-84°, has been isolated earlier by two groups of workers[10,11]. A survey of literature shows that the trisaccharide isolated is a new one. Its steroisomer namely 2-O-α-D-galacto pyranodyl-(1→2)-α-D-manno pyranosyl-(1→2)-D-mannose, $[\alpha]_D$ +110°, has been reported earlier[10]. The tetra saccharide appears to be a new compound since literature survey shows that no tetrasaccharide having this structure has been reported so far. The IR spectrum of the galactomannan exhibited bands at 820 and 880 cm^{-1} indicating the presence of both α- and β-glycosidic linkages[12,13]. From the foregoing results, tentative structure (I) showing one of the possible arrangements of sugar moieties in the repeating unit of polysaccharide may be advanced, which accommodates all the types of linkages present as mentioned above.

The structural studies on galactomannans have so far revealed, that majority of them possess a (1→4)-linked mannan backbone with galactosyl stubs attached to the backbone by (1→6)-linkage. *A. leucophloea* seed galactomannan differs from the general pattern in two important respects: (i) It carries a mixed main chain consisting of 33% galactose and 66% mannose residues, instead of mannose alone; and (ii) the constituent sugar units of the main chain are joined together by (1→2)-glycosidic linkages.

Though, the simultaneous occurrence of both galactose and mannose residues in the main chain has been encountered earlier in galactomannans from the seeds of *Phoenix dactylifera*[14], *Crotalaria juncea*[15], and *Cassia grandis*[16], the presence of (1→2)-glycosidic linkage in the main chain is an unique characteristic of *A. leucophloea* seed polysaccharide. This type of novel arrangement of main chain sugar residues in a seed galactomannan has been scarcely reported in the literature[17,18]. However, there are a number of galactomannans of microbial origin, e.g. from *Aspergillus niger*[19], *Cordiceps sinensis*[20] etc. which have been reported to possess (1→2)-linked mannan backbone.

Experimental Procedure

All evaporations were carried out under reduced pressure at 50-55°. Melting points are uncorrected and all optical rotations are equilibrium values. Paper chromatography was performed with the following solvent systems (v/v): (S_1) butanol-ethanol-water (4:1:5); (S_2) ethyl acetate-acetic acid-water (3:1:3); and (S_3) ethyl acetate-acetic acid-butanol-water (4:3:2:2). Whatmann No. 1 MM chromatographic paper was used for qualitative paper chromatography, and large amounts of sugar mixture were separated on 3 MM sheets. The following spray reagents were used for the detection of sugars: (R_1) acetonic silver nitrate-alcoholic sodium hydroxide; (R_2) *p*-anisidine phosphate; and (R_3) sodium metaperiodate-benzi dine-B. The IR spectra were recorded on a Perkin-Elmer infracord spectrophotometer model 137-B. Optronics high voltage paper electrophoresis apparatus was used for establishing homogeneity of the polysaccharide. A Hewlett-Packard gas chromatography apparatus (GC 5730 A) fitted with flame ionisation detector and columns packed with 3% of ECNSS-M on Gas Chrom Q (100-120 mesh) or 3% of OV-225 on Gas Chrom Q (100-120 mesh) was used for GLC.

Isolation of polysaccharide

Dried and crushed seeds of *A. leucophloea* (350 g) were extracted with pet ether (80-100) in order to obtain defatted material (208 g). A part of defatted material (100 g), was then stirred with water (1.3 litres) at 50-60° for 10 hr. The aqueous extract, after being acidified with acetic acid, was poured into large excess of ethanol with constant stirring to obtain light pink fibrous precipitate. This was repeatedly shaken with dry acetone and finally with ethanol until the precipitate became granular in nature (yield 10.3 g). The process of fractional precipitation with ethanol was repeated twice to furnish the polysaccharide as a white powder; yield 8.2 g; pentoses, 9.4%.

Purification of polysaccharide by copper complex formation with cupric acetate

An aqueous solution of white powder (8 g in 500 ml) was treated with 0.1 *M* sodium hydroxide (25 ml) and to the alkaline solution cupric acetate (5%, v/v) added slowly until the precipitation was complete. This upon centrifugation gave rise to a green solid (A) in low yield and a clear blue solution (B). Further decomposition of (A) with ice cold hydrochloric acid solution (0.05 *M*, 70 ml) followed by treatment with large excess of ethanol (400 ml) furnished a white precipitate, which was washed with ethanol and dried (yield 0.8 g). Acid hydrolysis of (A) furnished mainly xylose with traces of galactose and mannose, hence (A) appeared to be an impure xylan and therefore, was not investigated further.

The clear blue centrifugate (B) (480 ml) after acidification with acetic acid was poured into large excess of ethanol. The flocculent precipitate was triturated with dry acetone and absolute ethanol to yield the polysaccharide as a white granular powder (6.6 g). This was deionized by passing its aqueous solution through freshly regenerated cation and anion exchange resin columns. The combined effluent, after concentration, was precipitated with excess of ethanol. The white precipitate was filtered, washed with ethanol and dried; yield 5.8 g; $[\alpha]_D^{28}$ +22° (NaOH); IR (KBr): 3400 (br, OH), 2900 (s), 1650 (s), 880 (s) and 820 cm^{-1} (w).

Complete hydrolysis of polysaccharide

The purified polysaccharide was hydrolyzed with trifluoro acetic acid (2 *M*) at 100 for 13 hr. Paper chromatography (solvents S_1 and S_2) of the hydrolyzate revealed the presence of galactose and mannose only. The syrupy hydrolyzate was eluted with butanol half saturated with water from a column of cellulose to give (i) mannose [R_f 0.11 (S_1) and 0.19 (S_2)], $[\alpha]_D^{31}$ +14.5 , m.p. 131-32 ; *p*-nitro-N-phenyl-D-mannosyl amine derivative, m.p. and m.m.p. 216-17°; and (ii) galactose [R_f 0.07 (S_1) and 0.14 (S_2)], $[\alpha]_D^{31}$ +79.3 , m.p. 166-67 ; *p*-nitro-N-phenyl-D-galactosyl amine derivative, m.p. and m.m.p. 213-14°.

Quantitative estimation of individual sugars was carried out by periodate oxidation and phenol-sulphuric acid reagent and also by GLC of alditol acetates[3] using a 3% ECNSS-M column at 170°. The molar ratio of D-galactose and D-mannose was estimated to be 1:1.35.

Methylation of galactomannan

Galactomannan (5 g) was fully methylated by Haworth procedure[6] followed by Hakomori[7] method to yield the fully methylated polysaccharide (3.2 g; −OMe, 42.7%). The fully methylated polysaccharide (2.2 g) was dissolved in cold 72% sulphuric acid (10 ml) during 1 hr. The strength of acid solution was then reduced to 12% by the addition of calculated amount of water. The resulting mixture was heated on a boiling water-bath for 6 hr, cooled, neutralized, filtered and finally evaporated to a syrup (1.99 g). A portion (50 mg) of the syrup was converted into alditol acetate derivative in the usual way[21] and identified and estimated by GLC. The results are given in Table 1.

Table 1—GLC of Alditol Acetates of Partially Methylated Sugars on 3% of OV-225 Column at 170 C

Peak	O-Methyl sugar	RT	Peak area	Molar ratio
1	2,3,4,6-Tetra-O-methyl-D mannose	0.95	22505	1
2	2,3,4,6-Tetra-O-methyl-D-galactose	1.32	47770	2.12
3	3,4,6-Tri-O-methyl-D-mannose	1.86	100842	4.12
4	3,4,6-Tri-O-methyl-D-galactose	2.64	51072	2.08
5	3,4-di-O-methyl-D-mannose	3.76	50750	1.92
6	3,4-di-O-methyl-D-galactose	5.35	32780	1.24

Periodate oxidation and degradation of galactomannan

An aqueous solution of galactomannan (1.18 g, 100 ml) was treated with a cold solution of sodium metaperiodate (0.5 *M*, 20 ml) and the volume of resultant solution made up to 200 ml by the addition of water. The flask was kept in dark at 5-6°. The periodate consumption and formic acid liberated were estimated[22,23] at definite time intervals. After completion of the reaction (144 hr), the periodate consumed and formic acid liberated were observed to be 1.21 and 0.24 mol per hexose unit.

The remaining solution containing periodate-oxidized polysaccharide was treated with ethylene glycol (2 ml) (to destroy excess of sodium metaperiodate) and subsequently reduced with $NaBH_4$. The reaction mixture was acidified with acetic acid and kept overnight. The reduction product was then dialyzed, and distilled with methanol. The borate-free reduction product was hydrolyzed with sulphuric acid (0.5 *M*, 20 ml) for 8 hr. It was neutralized, filtered, deionized, and concentrated to a thin syrup, which upon paper chromatographic examination (solvent S_1 and spray reagent R_3) revealed a spot corresponding to glycerol.

Graded acid hydrolysis of galactomannan

Galactomannan (10 g) was heated on a water bath for 9 hr with 0.05 *M* sulphuric acid. The hydrolyzate, upon preparative partition chromatography (solvent S_3) furnished the following oligosaccharides:

(i) 2-O-β-D-Galactopyranosyl-D-mannose [m.p. 181-82, $[\alpha]_D$ +22 (water), R_{cello} 1.18 (solvent S_3)] upon acid hydrolysis furnished galactose and mannose. Sodium borohydride reduction and hydrolysis with acid furnished galactose only as a monosaccharide. Methyl glycoside derivative consumed 2.98 mol of sodium meta periodate with the liberation of 0.96 mol of formic acid. Acid hydrolysis of periodate oxidized compound gave glycerol only as indicated by paper chromatography.

(ii) 6-O-α-D-Galactopyranosyl-D-mannose {$[\alpha]_D^{31}$ +123°, m.p. 202° (lit[24] $[\alpha]_D$ +120-24°, m.p. 201-02), R_{cello} 1.09 (solvent S_3)}, upon acid hydrolysis gave galactose and mannose. However, after reduction with $NaBH_4$, glycoside derivative on oxidation with sodium metaperiodate liberated 1.90 mol of formic acid with simultaneous consumption of 3.92 mol of periodate. Upon Smith degradation it gave only glycerol.

(iii) 6-O-α-D-galactopyranosyl-D-galactose {$[\alpha]_D$ +145, m.p. 126° (lit[25,26] m.p. 130°, $[\alpha]_D$ +145°), R_{cello} 0.94 (solvent S_3)}, afforded galactose on acid hydrolysis. Methyl glycoside derivative consumed 3.96 mol of periodate with concomitant liberation of 1.98 mol of formic acid. Acid hydrolysis of periodate oxidized compound gave only glycerol.

(iv) O-β-D-Galactopyranosyl-(1→2)-β-D-manno pyranosyl-(1→2)-D-mannose {$[\alpha]_D^{31}$ +34.6°, R_{cello} 0.55 (solvent S_3)} on quantitative acid hydrolysis showed that it was built up of galactose and mannose in a molar ratio of 1:2. Periodate oxidation of methyl glycoside derivative showed consumption of 3.96 mol of oxidant with simultaneous liberation of 0.94 mol of formic acid. Periodate oxidized product after Smith degradation furnished only glycerol. Fully methylated product after acid hydrolysis produced 2,3,4,6-tetra-O-methyl-D-galactose and 3,4,6-tri-O-methyl-D-mannose in a molar ratio of 1:2.

(v) O-β-D-Galactopyranosyl-(1→2)-β-D-manno pyranosyl-(1→2)-D-mannopyranosyl-(1→2)-D-galactose {$[\alpha]_D^{31}$ +31 , m.p. 131-32°, R_{cello} 0.22 (solvent S_3)} on qualitative and quantitative acid hydrolysis showed that it was built up of galactose and mannose in equimolar proportions. Sodium metaperiodate oxidation of methyl glycoside derivative produced 0.94 mol of formic acid with simultaneous consumption of 4.90 mol of the reagent. The periodate oxidized product after Smith degradation furnished only glycerol. Fully methylated compound upon acid hydrolysis produced 2,3,4,6-tetra-O-methyl-D-galactose (1 mol) 3,4,6-tri-O-methyl-D-mannose (2 mol) and 3,4,6-tri-O-methyl-D-galactose (1 mol).

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Total Synthesis of Heterocyclic Steroids: Part VIII—Synthesis of (±)-8,13-Diazagona-5(10)-en-17-one & (±)-8,13-Diaza-6,6-dimethyl-2-thiagona-5(10)-en-17-one†

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Total syntheses of (±)-8,13-diazagona-5(10)-en-17-one (VII) and (±)-8,13-diaza-6,6-dimethyl-2-thiagona-5(10)-en-17-one (XX) have been achieved starting from 2-(cyclohexen-1-yl)ethylamine (I) and 2,2-dimethyl-2-[4-(5,6-dihydro-2*H*-thiopyranyl)]ethylamine (XVII) as their A-ring precursors respectively and 3-succinimidopropionyl chloride (II) as the common D-ring moiety. 2-(Cyclohexen-1-yl)ethylamine (I) and 2,2-dimethyl-2-[4-(5,6-dihydro-2*H*-thiopyranyl)]ethylamine (XVII) on condensation with succinimidopropionyl chloride (II) yield the corresponding N-[(2-cyclohexen-1-yl)ethyl]-3-succinimidopropionamide (III) and N-[(2,2-dimethyl-2-[4-(5,6-dihydro-2*H*-thiopyranyl)]ethyl]-3-succinimide (XVIII). The Bischler-Napieralski cyclisation of III gives a mixture of secosteroids (V) and (VI) which could not be separated. The crude mixture of V and VI on reductive cyclisation furnishes the steroid (VII). Similarly, the Bischler-Napieralski reaction of amide XVIII yields a secosteroid (XIX) which on reductive cyclisation furnishes the required steroid (XX).

In Part VII of this series[1], the total synthesis of (±)-8,13-diaza-3-thia-A-norgona-1,5(10)-dien-17-one was reported following the Taylor and Lenard route for the synthesis of (±)-2,3-dimethoxy-8,13-diazagona-1,3,5(10)-trien-17-one[2]. One of the key reactions in this route is the Bischler-Napieralski cyclisation of N-(3,4-dimethoxyphenethyl)-3-succinimidopropionamide to 3,4-dihydro-6,7-dimethoxy-1-(2-succinimidoethyl)isoquinoline for the construction of AB-rings of the 8,13-diazasteroid.

The reported Bischler-Napieralski cyclisation of ethyl N-[2-(cyclohexen-1-yl)]ethylmalonate to ethyl 3,4,5,6,7,8-hexahydro-1-isoquinolacetate[3] prompted us to utilize the readily accessible 2-(cyclohexen-1-yl)ethylamine (I)[4] and 2,2-dimethyl-2-[4-(5,6-dihydro-2*H*-thiopyranyl)]ethylamine (XVII) as the A-ring precursors in the total syntheses of 8,13-diazagona-5(10)-en-17-one (VII) and (±)-8,13-diaza-6,6-dimethyl-2-thiagona-5(10)-en-17-one (XX) with 3-succinimidopropionyl chloride (II)[5] as the common D-ring moiety.

An endocyclic double bond in the A-ring precusor as a prerequisite for the successful synthesis of VII would enable an introduction of any hetero atom in the A-ring. Hence in the synthesis of XX we made use of readily accessible tetrahydrothiopyran-4-one (VIII), which would reasonably be transformed into 2-[4-(5,6-dihydro-2*H*-thiopyranyl)]ethylamine (XIV) to serve as a A-ring precursor.

Thus, the amine (I) was condensed with 3-succinimidopropionyl chloride (II) in dry tetrahydrofuran in the presence of pyridine to afford N-[(2-cyclohexen-1-yl)ethyl]-3-succinimidopropionamide (III) in 57% yield. The amide (III) on Bischler-Napieralski reaction gave a mixture of two products (TLC). The separation of the mixture into the individual components was not possible as one of the products was found to decompose on purification by column chromatography. The mixture showed a prominent molecular ion peak at (M^+ 260) which could be attributed to one of the possible three cyclodehydrated products (IV), (V) or (VI) obtainable from the amide (III). The UV spectrum in MeOH exhibited absorption maxima at 263 (log ε 3.29) and 271 (log ε 3.27) nm which might be due to the N-vinylsuccinimido system. The IR spectrum in $CHCl_3$ displayed bands at 1786 and 1695 cm^{-1} which were attributed to the succinimido carbonyls. In the PMR spectrum in $CDCl_3$ a singlet at δ 2.70 could be attributed to N-substituted succinimido protons and two doublets centred at 6.89 ($J = 5$ Hz) and 8.23 ($J = 5$ Hz) to vinyl protons of the N-vinylsuccinimido moiety. Further, there was no signal in the vinyl region. Hence from the spectral data it could be concluded that out of the three probable compounds obtainable, the mixture contained 8,13-diaza-8,14-seco-gona-5(10),11-diene-14,17-dione(V) and 8,13-diaza-8,14-seco-gona-5(10),8-diene-14,17-dione (VI) as the major products.

†All the compounds in the synthetic sequence are racemic. To clarify the stereochemical presentation, only one enantiomer is depicted.
‡This paper forms a part of the Ph.D. thesis of S H T submitted to the University of Bombay in 1982.

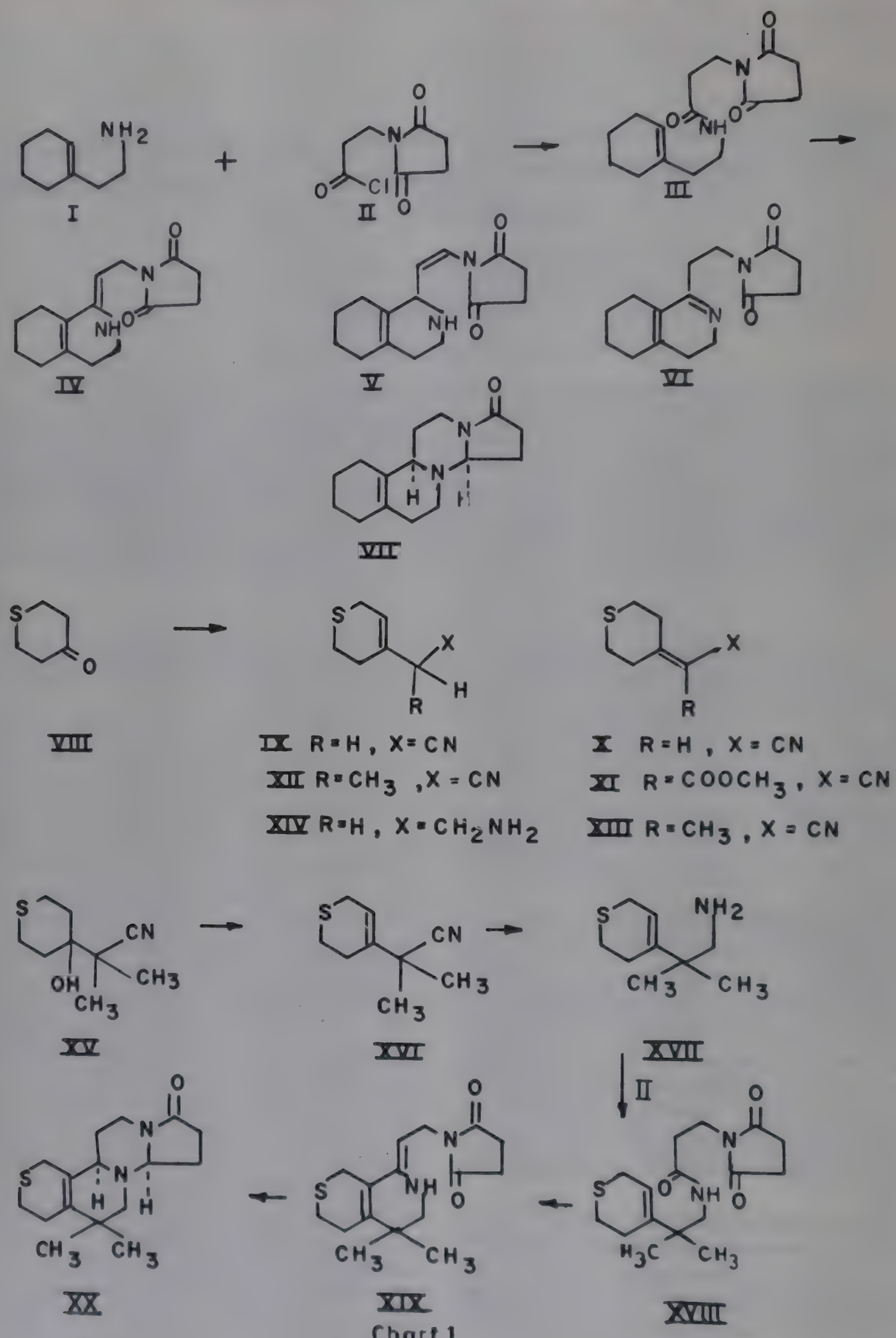

Chart 1

The corresponding amide (XVIII) of the steroid (XX) was prepared by adopting the following procedure: The pyrrolidine enamine of tetrahydrothiopyran-4-one (VIII) on treatment with cyanoacetic acid in dioxane gave contrary to expectation[6] a mixture of the endonitrile, 4-(5,6-dihydro-2*H*-thiopyranyl)acetonitrile (IX) and exonitrile 4-(tetrahydrothiopyrilidine)acetonitrile (X) in 80% yield in the ratio

30:70 as revealed by GLC. It was then thought that the replacement of one of the hydrogens of the carbon atom alpha to the cyano group by the methyl group in cyanoacetic acid, would give a product which might give the corresponding endo-nitrile in better yield. Hence, the ketone (VIII) was treated with methyl-2-methylcyanoacetate under Knoevanagel reaction conditions to give methyl 2-(4-tetrahydrothiopyrilidine)cyanoacetate (XI) in good yield. Methylation of ester (XI) followed by decarboxylation of the product formed gave 2-[4-(5,6-dihydro-2*H*-thiopyranyl)]propionitrile (XII) and 2-(4-tetrahydrothiopyrilidine) propionitrile (XIII) in the ratio 1:2. Apparently, this route also provided the desired endo-nitrile (XII) in lower yield. It could thus be concluded that in the thiopyranyl ring, the exo double bond is favoured to the endo in the nitriles.

To circumvent this difficulty it was necessary to substitute in cyanoacetic acid both the hydrogen atoms on the carbon atom alpha to the cyano group by methyl groups. Thus, the Reformatski reaction of 2-methyl-2-bromopropionitrile[7] on the ketone (VIII) was carried out in the presence of zinc and a catalytic amount of mercuric chloride to give 2-methyl-2-[4-(4-hydroxytetrahydrothiopyranyl)]propionitrile (XV) in 67% yield as a viscous oily liquid which solidified on standing. The tertiary alcohol (XV) was dehydrated to 2-methyl-2-[4-(5,6-dihydro-2*H*-thiopyranyl)] (XVI) in 80% yield by treatment with phosphorus oxychloride in pyridine. The IR and PMR spectral data agreed well with the structure assigned. The nitrile (XVI) was reduced to 2,2-dimethyl-2-[4-(5,6-dihydro-2*H*-thiopyranyl)]ethylamine (XVII) in 94% yield, which formed the A-ring precursor for the synthesis of XX. Amine (XVII) decomposed on standing.

The dihydrothiopyranylethylamine (XVII) on condensation with 3-succinimidopropionyl chloride (II) in dry tetrahydrofuran in the presence of pyridine gave N-[2,2-dimethyl-2-[4-(5,6-dihydro-2*H*-thiopyranyl)]ethyl]-3-succinimide (XVIII) (M^+ 324), in 56% yield.

The amide (XVIII) on Bischler-Napieralski reaction gave 8,13-diaza-6,6-dimethyl-2-thia-8,14-seco-gona-5(10), 9(11)-diene-14,17-dione (XIX) (M^+ 306) in 95% yield. The TLC analysis of this crude product indicated it to be a single compound. Spectral analyses (IR, PMR) of crude product also indicated that secosteroid (XIX) was present in the crude product. However, purification of this crude product proved difficult as attempted distillation under reduced pressure resulted in its decomposition to succinimide. It was also difficult to purify it by column chromatography and hence it was used as such for further transformation.

The crude mixture of secosteroids (V) and (VI) obtained from III was reductively cyclised by hydrogenation over platinum oxide catalyst at 50 psi. The TLC analysis of the product showed the presence of two compounds, one of which was found to be the unchanged secosteroid (V). The separation of the mixture was achieved by column chromatography. The compound having R_f 0.6 (M^+ 260) was fully characterized by its UV, IR and PMR data as V. The compound having R_f 0.4 (M^+ 246) was fully characterized on the basis of its IR and PMR data as 8, 13-diazagona-5(10)-en-17-one (VII). It exhibited in its IR spectrum bands at 2740, 2667 (Bohlmann bands)[8] and 1681 cm^{-1} (C=O). Likewise, the secosteroid (XIX) on reductive cyclisation gave 8,13-diaza-6,6-dimethyl-2-thiagona-5(10)-en-17-one (XX) (M^+ 292) in 52% yield.

The sterochemistry of the diazasteroids (VII) and (XX) was assigned on the basis of IR and PMR spectral data and by analogy with the work of Redeuilh and Viel[9] on the synthesis of (±)-2,3-dimethoxy-8,13-diazagona-1,3,5(10)-trien-17-one. The characteristic Bohlmann bands[8] in VII appear at 2740 and 2667 cm^{-1} while in XX these appear at 2874 and 2817 cm^{-1}. Also the upfield shift for the C-9 proton in the PMR spectra[10] of VII and XX suggested the B/C-*trans* ring fusion in these diazasteroids. The multiplets centred at δ 3.86 and 4.18 in the PMR spectrum of VII and at 4.09 and 4.35 in the case of XX were attributed to the C-14 proton and the C-12 equatorial proton by analogy with the assignment made to the signals at 4.05 and 4.34 of the A-benzonoid-8,13-diazasteroid[9] by Redeuilh and Viel. The same analogy was further extended to the C/D-*trans* ring fusion and the overall configuration as *trans-anti-trans* was assigned to VII and XX since the same sequence of reactions was employed in their synthesis.

Experimental Procedure

For bulb tube distillation, air bath temperature is given as the boiling point. Recorded temperatures are uncorrected. IR spectra were taken on a Perkin-Elmer infracord spectrophotometer model 137B as films or solutions in chloroform in the case of liquids and as potassium bromide pellets for solid simples. UV spectra were determined on a Carl-Zeiss spectrophotometer RPQ-20 A as solution in methanol. PMR spectra were recorded in $CDCl_3$ or CCl_4 on a Varian A-60A spectrometer using TMS as an internal standard (chemical shifts in δ-values). Mass spectra were recorded on VG Micromass model 7070F. Refractive indices were taken using Bausch and Lamp refractometer model ABBE-31. Silica gel (<0.08 mm) was used for column chromatography. Anhydrous sodium sulphate was employed as a drying agent.

N-[2-(*Cyclohexen*-1-*yl*)*ethyl*]-3-*succinimidopropionamide* (*III*)

To a solution of 2-(cyclohexen-1-yl)ethylamine (I) (8.7 g, 0.07 mol) and dry pyridine (5 ml) in dry tetrahydrofuran (40 ml) was added a solution of 3-succinimidopropionyl chloride (II) [prepared from 3-succinimidopropionic acid (11.98 g, 0.07 mol) and thionyl chloride (50 ml, 0.7 mol)] in dry tetrahydrofuran (40 ml) at 0° under nitrogen atmosphere. After the addition was over, the solution was brought to room temperature and stirred overnight. It was then decomposed by pouring on ice-cold water and extracted with chloroform (3 × 40 ml). The combined organic layer was washed with hydrochloric acid (10%, 3 × 20 ml) followed by brine and dried. The solvent was evaporated on a water-bath to afford a crude dark coloured product (18 g) which was chromatographed over silica gel (200 g, eluent: 20% acetone in chloroform). Fractions showing a single spot on the TLC were mixed and the solvent was removed to get the pure amide (III) which was further purified by crystallisation from ethyl acetate, m.p. 164° (11 g, 56.9%). The analytical sample was prepared by recrystallisation from ethyl acetate; m.p. 165°; IR: 3356 (amide NH), 2955, 1788, 1724 (succinimido carbonyls)[11], 1639 (amide C=O), 1563, 1420, 1242, 1163 cm^{-1}; PMR($CDCl_3$): 2.72 (4H, *s*, $O=\overset{|}{C}-CH_2-CH_2-\overset{|}{C}=O$), 5.55 (2H, *m*, vinyl and amide protons); MS: *m/z* 278 (M^+) (Found: C, 64.4; H, 8.2; N, 10.2. $C_{15}H_{22}N_2O_3$ requires C, 64.7; H, 8.0; N, 10.1%).

2-*Methyl*-2-[4-(4-*hydroxytetrahydrothiopyranyl*)]-*propionitrile* (*XV*)

To a mixture of tetrahydrothiopyran-4-one (VIII) (5.8 g, 0.05 mol) and mercuric chloride (0.17 g) in benzene (60 ml) was added 2-methyl-2-bromopropionitrile (8.88 g, 0.06 mol) and zinc (16.3 g, 0.25 g atom) in three lots at an interval of 1 hr, each time maintaining the mixture at the reflux temperature. After the addition was complete, the mixture was further refluxed for 3 hr, cooled, decomposed by pouring into ice-cold sulphuric acid (10%, 200 ml) and stirred for about 10 min. The benzene layer was separated and the aq portion was extracted with ether-benzene (3 × 50 ml, 1:1). The organic extracts were combined, the combined extract was washed with a saturated aq sodium bicarbonate (2 × 20 ml), washed free from the base, dried and the solvent evaporated on a water-bath. The residual oily hydroxynitrile (XV) was distilled at 120-22°/0.25 mm (6.18 g, 66.8%). The product solidified on standing. The analytical sample was prepared by recrystallisation from benzene-pentane (35-37°); m.p. 59°; IR: 3546 (OH), 2941, 2247 (C≡N), 1429, 1370, 1200, 1081, 935 cm^{-1}; PMR (CCl_4): 1.37 (6H, *s*, $H_3C-\overset{|}{C}-CH_3$), 2.52 (1H, D_2O exchangeable, OH); MS: *m/z* 185 (M^+) (Found: C, 58.2; H, 8.2; N, 7.8; S, 17.0. $C_9H_{15}NOS$ requires C, 58.4; H, 8.2; N, 7.6; S, 17.3%).

2-*Methyl*-2-[4-(5,6-*dihydro*-2*H*-*thiopyranyl*)]-*propionitrile* (*XVI*)

To a cooled solution of XV (2.78 g, 15 mmol) in pyridine (30 ml), freshly distilled phosphorous oxychloride (14 ml, 0.15 mol) was added and the reaction mixture refluxed for 5 hr. It was cooled, decomposed cautiously by pouring onto crushed ice, extracted with ether-benzene (3 × 30 ml, 1:1), the combined organic extract washed first with hydrochloric acid (10%, 3 × 20 ml) followed by brine. After drying, the solvent was evaporated on a water-bath and the product was distilled at 95-100° (air-bath)/0.1 mmHg, to give a colourless liquid (2 g, 79.7%). The analytical sample was prepared by redistillation at 95-100° (air-bath)/0.1 mm; η_D^{26} 1.5195; IR: 2985, 2924, 2247 (C≡N), 1471, 1429, 1370, 1299, 1220, 885, 797 cm^{-1}; PMR(CCl_4): 1.47 (6H, *s*, $H_3C-\overset{|}{C}-CH_3$), 6.07 (1H, *m*, vinyl proton); MS: *m/z* 167 (M^+) (Found: C, 64.5; H, 7.6; N, 8.6; S, 18.5. $C_9H_{13}NS$ requires C, 64.6; H, 7.8; N, 8.4; S, 19.1%).

2,2-*Dimethyl*-2-[4-(5,6-*dihydro*-2*H*-*thiopyranyl*)]-*ethylamine* (*XVII*)

To a suspension of LAH (4.4 g, 0.12 mol) in anhydrous ether (50 ml) was added dropwise, a solution of XVI (4.18 g, 25 mmol) in anhydrous ether (50 ml) under N_2 during 0.5 hr. After the addition was complete, the reaction mixture was refluxed for 3.5 hr, cooled, excess LAH destroyed and then a solution of sodium potassium tartrate (30 g) in water (100 ml) added to it. The ether layer was separated and the aqueous portion extracted with ether-benzene (4 × 50 ml, 1:1). The combined organic layer was dried, the solvent evaporated on a water-bath and crude amine (XVII) distilled at 140-42°/0.5 mm (4 g, 93.5%); η_D^{25} 1.5350; IR: 3333 (NH_2), 2899, 1449, 1408, 1351, 1282 cm^{-1}; PMR (CCl_4): 0.98 (6H, *s*, $H_3C-\overset{|}{C}-CH_3$), 1.20 (2H, *s*, D_2O exchangeable, primary amine protons), 5.72 (1H, *m*, vinyl proton); MS: *m/z* 171 (M^+); XVII.HCl, m.p. 138° (d). The analytical sample of XVII.HCl was prepared by recrystallisation from ethyl acetate, m.p. 140° (d) (Found: C, 52.0; H, 8.6; N, 6.9; S, 15.2; Cl, 17.1. $C_9H_{18}ClNS$ requires C, 52.0; H, 8.7; N, 6.7; S, 15.4; Cl, 17.1%).

N-[2,2-*Dimethyl*-2-[4-(5,6-*dihydro*-2*H*-*thiopyranyl*)]*ethyl*]-3-*succinimidopropionamide* (*XVIII*)

To a solution of XVII (2.57 g, 15 mmol) and pyridine (1.5 ml) in dry tetrahydrofuran (20 ml) was added

dropwise a solution of 3-succinimidopropionyl chloride (II) [prepared from 3-succinimidopropionic acid (2.84 g, 15 mmol) and thionyl chloride (22 ml, 0.3 mol)] in dry tetrahydrofuran (20 ml) at 0° under nitrogen atmosphere. After the addition was over the solution was stirred overnight, decomposed by pouring into ice-cold water and extracted with chloroform (3 × 20 ml). The combined organic layer was washed with hydrochloric acid (10%, 3 × 20 ml) followed by brine and dried. The solvent was evaporated on a water-bath to give the crude dark coloured product (4.5 g) which was chromatographed over silica gel (100 g, eluent: 20% acetone in chloroform). Fractions showing a single spot on the TLC were mixed together and the solvent was removed to give a pure compound which was crystallised from ethyl acetate, m.p. 139° (2.74 g, 56.3%). The analytical sample of XVIII was prepared by recrystallisation from ethyl acetate, m.p. 140°; IR (KBr): 3333 (amide NH), 3125, 2985, 1788, 1698 (succinimido carbonyls)[6], 1642 (amide C=O), 1565, 1379, 1250, 1164, 1107 cm^{-1}; PMR ($CDCl_3$): 1.05 (6H, *s*, $H_3C-\overset{|}{C}-CH_3$), 2.75 (4H, *s*, $O=\overset{|}{C}-CH_2-CH_2-\overset{|}{C}=O$), 5.80 (2H, *m*, vinyl and amide protons); MS: *m/z* 324 (M^+) (Found: C, 59.1; H, 7.3; N, 8.4; S, 10.1. $C_{16}H_{24}N_2O_3S$ requires C, 59.2; H, 7.5; N, 8.6; S, 9.9%).

Bischler-Napieralski cyclisation of N-[2-(cyclohexen-1-yl)ethyl]-3-succinimidopropionamide (III): Formation of 8,13-diaza-8,14-seco-gona-5(10),11-diene-14,17-dione (V) and 8,13-diaza-8,14-seco-gona-5(10),8-diene-14,17-dione (VI)

To a solution of III (0.975 g, 3.5 mmol) in dry methylene chloride (40 ml) was added phosphorous pentoxide (5 g, 35 mmol) in 3-4 lots with stirring under N_2 and the reaction mixture was left overnight. Next day, after refluxing for 1 hr it was cooled and decomposed by adding ice-cold water. The organic layer was separated and extracted with hydrochloric acid (10%, 2 × 10 ml). The acidic extracts and the original aq. portion were mixed together and extracted with chloroform (2 × 50 ml) to remove the unchanged amide (III). The acidic portion was then basified with sodium carbonate and extracted with chloroform (4 × 20 ml). After drying, the solvent was removed on a water-bath when a dark coloured viscous liquid (0.865 g) was obtained. The TLC analysis (silica gel-30% acetone in ethyl acetate, one run) revealed that the crude product consisted of the secosteroids (V) and (VI). However, when the separation was attempted, one of the secosteroids was found to decompose on the column and hence the mixture (M^+ 260) was used as such for the further transformation; IR: 2941, 1786, 1695 (succinimido carbonyls), 1600, 1399, 1220, 1556 cm^{-1}; UV: 263 nm (log ε 3.29), 271 nm (log ε 3.27); PMR ($CDCl_3$): 2.70 (4H, *s*, $O=\overset{|}{C}-CH_2-CH_2-\overset{|}{C}=O$), 6.89 (1H, *d*, $J=5$ Hz) and 8.23 (1H, *d*, $J=5$ Hz vinyl protons).

Bischler-Napieralski cyclisation of N-[2,2-dimethyl-2-[4-(5,6-dihydro-2H-thiopyranyl)]ethyl]-3-succinimidopropionamide (XVIII): 8,13-Diaza-6,6-dimethyl-2-thia-18,14-seco-gona-5(10),9(11)-diene-14,17-dione (XIX)

To a solution of XVIII (0.97 g, 3 mmol) in xylene (dried over sodium, 30 ml) was added phosphorous pentoxide (7 g, 0.05 mol) in three lots at an interval of 0.5 hr under nitrogen atmosphere at a reflux temperature. After the addition was over, the reaction mixture was further refluxed for 3 hr. It was then cooled and decomposed cautiously by adding ice-cold water, the aqueous layer separated and the xylene layer extracted with hydrochloric acid (10%, 2 × 5 ml). The aqueous layer and the acid washings were mixed together and extracted with chloroform (2 × 20 ml) to remove the unreacted starting amide (XVIII). The aqueous portion was basified with sodium carbonate and extracted with chloroform (3 × 50 ml) and dried. Removal of the solvent on a water-bath gave a dark coloured liquid (M^+ 306) (0.88 g, 94.4%). On TLC the crude product showed a single spot. However, all attempts to purify this secosteroid (XIX) proved futile as it decomposed to succinimide when distillation under high vacuum was attempted. It was also found to decompose on chromatographic columns and hence was used as such for further transformation; IR: 2985, 1792, 1709 (succinimido carbonyls), 1626, 1408, 1170 cm^{-1}; PMR ($CDCl_3$): 1.27 (6H, *s*, $H_3C-\overset{|}{C}-CH_3$), 2.72 (4H, *s*, $O=\overset{|}{C}-CH_2-CH_2-\overset{|}{C}=O$), 5.65 (1H, *m*, vinyl proton).

Reductive cyclisation of a mixture of the secosteroids (V) and (VI): Formation of 8,13-diazagona-5(10)-en-17-one (VII)

A mixture of the secosteroids (V) and (VI) (0.91 g) obtained above was hydrogenated over platinum oxide (100 mg) in ethanol (20 ml) at 53 psi for 17-18 hr. The catalyst was filtered and the solvent removed on a water-bath to give crude product (0.9 g). The TLC analysis (silica gel, 30% acetone in ethyl acetate) showed the presence of secosteroid (V) and VII. The mixture was chromatographed over silica gel (150 g, eluent: 10% acetone in ethyl acetate). Fractions were collected and monitored by TLC (silica gel, 30% acetone in ethyl acetate). Fractions showing a single spot on TLC were combined and the solvent removed on a water-bath. The secosteroid (V) was separated as a colourless liquid and was distilled at 185-90° (air-

bath)/0.05 mm (0.12 g). Similarly the diazasteroid (VII) was separated and was distilled at 145-50° (air-bath)/0.05 mm (0.35 g).

The analytical sample of V was prepared by redistillation at 180-85° (air-bath)/0.05 mm, η_D^{25} 1.5510; IR: 3521 (NH), 2985, 1788, 1709 (succinimido carbonyls), 1603, 1408, 1159, 823 cm^{-1}; UV: 264 nm (log ε 3.45), 271 nm (log ε 3.39); PMR ($CDCl_3$): 2.68 (4H, *s*, $O=\overset{|}{C}-CH_2-CH_2-\overset{|}{C}=O$), 3.58 (1H, *m*, N*H*), 6.91 (1H, *d*, $J=5$ Hz, vinyl proton) and 8.23 (1H, *d*, $J=5$ Hz, vinyl proton); MS: *m/z* 260 (M^+) (Found: C, 69.2; H, 7.6; N, 10.8. $C_{15}H_{20}N_2O_2$ requires C, 69.2; H, 7.7; N, 10.8%).

The analytical sample of VII was prepared by redistillation at 140-45° (air-bath)/0.05 mm; η_D^{25} 1.5470; IR: 2899, 2740, 2667 (Bohlmann bands), 1681 (C=O), 1439, 1361, 1299, 1266 cm^{-1}; PMR ($CDCl_3$): 3.86 (1H, *m*, C-14 proton), 4.18 (1H, *m*, C-12 equatorial proton); MS: *m/z* 246 (M^+) (Found: C, 72.9; H, 8.9; N, 11.5. $C_{15}H_{22}N_2O$ requires C, 73.1; H, 9.0; N, 11.4%).

8,13-*Diaza*-6,6-*dimethyl*-2-*thiagona*-5(10)-*en*-17-*one* (*XX*)

The secosteroid (XIX) (0.2 g, 0.65 mmol) was hydrogenated over platinum oxide catalyst (100 mg) at 40-50 psi in ethanol (40 ml) for 24 hr. After the hydrogenation was complete, the catalyst was filtered and the solvent removed on a water-bath to give a crude product (0.16 g) which was chromatographed over silica gel (30 g, eluent: 20% acetone in ethyl acetate). Fractions showing a single spot on the TLC were mixed and the solvent removed to give a light yellow coloured solid (0.1 g, 52.4%). It was crystallised from benzene-pet. ether (60-80°) to afford XX as a light yellow coloured compound, m.p. 133°. The analytical sample was prepared by recrystallisation from benzene-pet. ether (60-80°); m.p. 134°; IR: 2985, 2874, 2817 (Bohlmann bands), 1701 (C=O), 1449, 1425, 1389, 1299, 1250, 1136 cm^{-1}; PMR (CCl_4): 1.28 (6H, *s*, $H_3C-\overset{|}{C}-CH_3$), 4.09 (1H, *m*, C-14 proton), 4.35 (1H, *m*, C-12 equatorial proton); MS: *m/z* 292 (M^+) (Found: C, 65.5; H, 8.4; N, 9.6; S, 11.1. $C_{16}H_{24}N_2OS$ requires C, 65.7; H, 8.3; N, 9.6; S, 10.9%).

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Studies on Azomethine Rearrangements Involving 1-Benzoyl-*cis*-bicyclo[3.3.0]octane & Its Oxime

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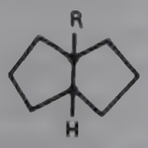
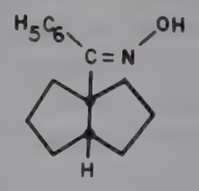
1-Benzoyl-*cis*-bicyclo[3.3.0]octane(**2**) is prepared and converted to the oxime(**3**) of which two geometrical isomers, *E*-(**11**) and *Z*-(**12**) are obtained. The oxime(**11**) on Beckmann rearrangement in several reagents such as conc. H_2SO_4, PPA, PCl_5 and HCO_2H remains unaffected whereas the isomeric oxime(**12**) gives *cis*-bicyclo[3.3.0]oct-1-anilide (N-phenyl-*cis*-bicyclo[3.3.0]oct-1-amide) (**9**). The ketone(**2**) on Schmidt reaction provides the N-*cis*-1-bicyclo[3.3.0]octylbenzamide (**10**) but not the anilide (**9**). The identity of the products obtained from the Beckmann rearrangement of the oxime(**12**) and the Schmidt reaction of **2** has been established by unambiguous synthesis.

Azomethine rearrangements involving bridgeheads of condensed ring systems such as bicyclo[2.2.1]heptyl, [2.2.2]octyl and adamantyl systems are known[1]. However, not much information seems to be available on the rearrangements of bridgeheads of *cis*-bicyclo[3.3.0]octyl (*cis*-pentalanyl) system. Further, it has been recognized that certain ketoximes having α-tri- or α-tetra-substituted alkyl substituents on a bridgehead system are capable of forming relatively stable carbocation and instead of normal Beckmann rearrangement[2-4] these compounds undergo Beckmann fragmentation[4-12]. Fischer and Grob[11] have shown that the bicyclo[2.2.2]octyl group peregrinates in the Beckmann rearrangement. On the otherhand Hill and Chortyk[9] have shown the first violation to the rule of retention of configuration of migrating group and as a consequence presented an alternate two-step 'fragmentation-recombination' mechanism for Beckmann reaction of 9-acetyl-*cis*-decalin oxime in strong acid media.

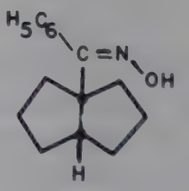
In the background of these interesting observations, the Beckmann rearrangement of the oxime (**5**) of 1-acetyl-*cis*-bicyclo[3.3.0]octane(**4**) in which the functional group $>C=NOH$ is at the bridgehead of *cis*-pentalanyl system was recently reported by us[13]. It was shown that the intermediacy of a two-step mechanism of Hill and Chortyk seems to intrude in preference to the normal 'concerted' mechanism since the structural features of **5** favour its fragmentation to a stable 3 cation and acetonitrile which in turn would then recombine by a Ritter-type reaction leading to the products (**6**) and (**7**). In order to see whether this mechanism intrudes in the case of bridgehead oximes having aryl groups, further investigations on azomethine rearrangements of 1-benzoyl-*cis*-bicyclo-[3.3.0]octane(**2**) and its oxime(**3**) have now been



1 R = $-CO_2H$ 6 R = $-NHCOCH_3$
2 R = $-COC_6H_5$ 7 R = $-H$
3 R = $-C(C_6H_5)=NOH$ 8 R = $-NH_2$
4 R = $-COCH_3$ 9 R = $-CONHC_6H_5$
5 R = $-C(CH_3)=NOH$ 10 R = $-NHCOC_6H_5$



11



12

carried and the results are reported in the present paper.

The ketone(**2**) was prepared[15] from the acid chloride of *cis*-bicyclo[3.3.0]octane-1-carboxylic acid(**1**). The preparation of the oxime(**3**), of which two geometrical isomers (*E* and *Z*) are possible, was carried under various conditions. Among the methods tried for **3** the procedure of Fischer and Grob[11] was not only found satisfactory but also provided under varying conditions, two isomeric oximes, melting at 67-68°C and 135°. It was observed that the reaction time of 40 hr provided a maximum yield of the low melting oxime (70%) whereas the higher melting oxime was obtained in 85% yield when the reaction time was 80 hr beyond

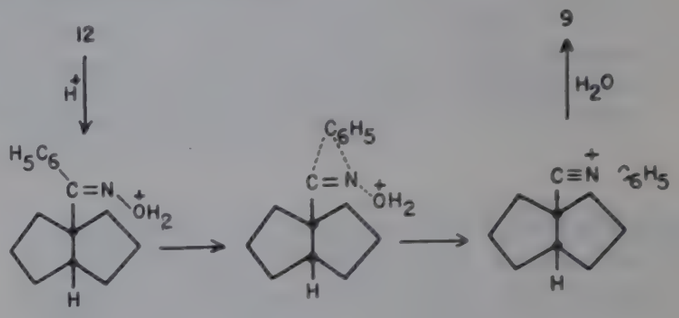
which the yield of the latter did not improve. On the other hand following the procedure of Hill *et al.*[6] (reflux at 95-100° for 60 hr) an oily mixture of products was obtained from **2**. When the product mixture was distilled under reduced pressure and the fractions purified by column chromatography, homogeneous samples of low and high melting oximes were obtained in 20% and 47% yields respectively. It appears quite likely that there occurs *syn-anti* conversion and the higher melting one is thermodynamically stable. On the basis of the examinations of models the phenyl group occupying the *anti-* position to the hydroxyl group appears to be sterically favourable than the oxime with *syn*-phenyl group. Thus the higher melting oxime is the *anti*-phenyl-1-*cis*-bicyclo[3.3.0]octyl oxime or the *Z*-isomer(**12**) whereas the low melting oxime is the *syn*-phenyl-1-*cis*-bicyclo[3.3.0]octyl oxime or the *E*-isomer (**11**). The configurations assigned are supported by Beckmann rearrangement as well as other observations.

The Beckmann reaction of **11**, studied in conc. H_2SO_4, PPA, PCl_5 or HCO_2H, did not yield any rearranged product but was recovered quantitatively. It is quite likely that the stereo-electronic factors in **11** are not favourably disposed to allow. usual protonation or acylation of the oximino-hydroxyl group with consequent absence of rearrangement. On the otherhand the ketoxime(**12**) underwent Beckmann rearrangement in the presence of aforementioned reagents leading to the formation of single isolable product, m.p. 145-46°. The product of rearrangement would be either *cis*-bicyclo[3.3.0]oct-1-anilide(**9**) or N-*cis*-1-bicyclo[3.3.0]octylbenzamide(**10**). In order to establish the identity of the Beckmann product of authentic samples of **9** and **10** were prepared (see Experimental) . The Beckmann product of the oxime (**12**) was identical in all respects (m.p., m.m.p., co-TLC, IR, PMR) with the anilide (**9**). The percentage yields of the product (**9**) from the Beckmann reaction of the oxime (**12**) under various conditions are given in Table 1. The foregoing experiments evidently demonstrate that the oxime (**12**) in which the phenyl group is *anti-*, affords **9** under normal Beckmann mechanism of concerted pathway involving *anti* migration of phenyl group with concomitant formation of **9** (Scheme 1). This is in contrast to our earlier observations of the Beckmann rearrangement of the acetyl oxime (**5**) in which the two-step mechanism involving fragmentation-recombination pathway was shown to be operative.

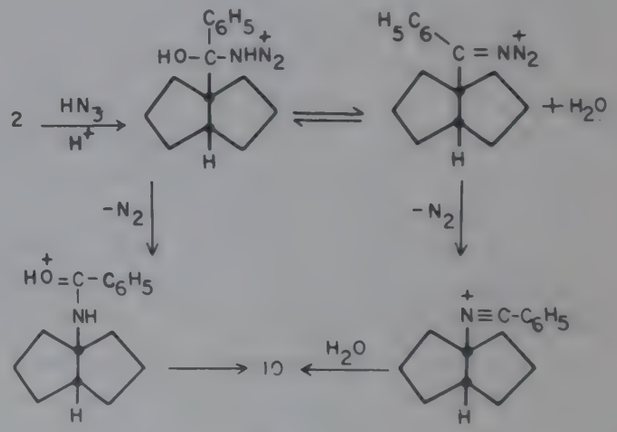
In another series of experiments the parent bridgehead ketone(**2**) was subjected to Schmidt rearrangement[16-18] in which it was allowed to react with hydrazoic acid generated from sodium azide and sulphuric acid or PPA under various conditions leading

Table 1 – Percentage Yield of Product (**9**) from Beckmann Rearrangement of Oxime(**12**) under Various Conditions

Sl. No.	Reagent	Conditions	Yield of **9** (%)
1	PPA	25°, 10 hr	55
		40°, 48 hr	55
		125°, 15 min	45
		150°, 1 hr	50
2	H_2SO_4(98%)	30°, 15 hr	60
	H_2SO_4(85%)	110°, 15 min	55
3	HCO_2H	140°, 6 hr	70
4	PCl_5	35°, 14 hr	65



Scheme 1



Scheme 2

to the formation of a single isolable product, which was found to be N-*cis*-1-bicyclo[3.3.0]octylbenzamide(**10**), m.p. 119°, in varying yields 44-56%. The identity of **10** was established by direct comparison (m.p., m.m.p., co-TLC, IR, PMR) with the sample obtained by benzoylation of **8**[13,14]. The rearrangement of **2**, a cycloalkyl aryl bridgehead ketone, under the Schmidt conditions seems quite likely to follow the pathways shown in Scheme 2, in which the bulky bicyclooctyl group would generally undergo migration with retention of configuration leading to the formation of **10**. This is in confirmity with the general trend of the alkyl-aryl ketones in undergoing Schmidt reaction in which the product formation depends very much on the nature of the alkyl substitutents. It should be mentioned here that the Schmidt reaction of the bridgehead ketone(**4**)[19] under analogous conditions

furnished the amide(**6**), in confirmity with the foregoing observation. The Schmidt reaction of bridgehead ketones not only needs mild conditions but may also have advantages in converting these ketones readily into amides without affecting the other substituent groups attached to either bicyclooctyl or to the aryl group.

The foregoing results illustrate the apparent diversity of reactivity amongst the bridgehead ketoximes such as **3** and **5** under Beckmann conditions while demonstrating the synthetic utility of the azomethine reactions involving the bridgehead functional groups of the *cis*-pentalanyl system.

Experimental Procedure

Melting points were determined in open capillaries and are uncorrected. IR spectra in KBr were recorded on a Beckmann-Aculab 10 spectrophotometer (ν_{max} in cm^{-1}), and PMR spectra in $CDCl_3$ on a Perkin-Hitachi R-24 instrument using TMS as an internal standard (chemical shifts in δ ppm). TLC was carried out on glass plates coated with silica gel G (Stahl, type 60) and spots were visualized by exposure to iodine vapours.

1-Benzoyl-*cis*-bicyclo[3.3.0]octane(**2**) was prepared by treatment of the acid chloride of *cis*-bicyclo-[3.3.0]octane-1-carboxylic acid(**1**) with diphenyl-cadmium or alternatively via the Grignard synthesis with phenylmagnesium bromide following the procedure reported earlier by us[15].

E-Phenyl-1-cis-bicyclo[3.3.0]*octyl oxime*(**11**) *and Z-Phenyl-1-cis-bicyclo*[3.3.0]*octyl oxime*(**12**)

Following the procedure of Fischer and Grob[11] a mixture of **2** (2.4 g), hydroxylamine hydrochloride (2.4 g) and potassium hydroxide (2.4 g) in ethanol (95%; 70 ml) was refluxed at 95° for 40 hr. Ethanol was distilled off, the residue diluted with ice-water (50 ml), acidified with dil HCl, extracted with ether, the ether extract washed with water, dried ($MgSO_4$) and concentrated. The crude reaction product was purified by passing through an alumina column. Elution with benzene removed the unreacted **2** (7%) while elution with ethyl acetate provided **11** (70%) which on crystallization from cyclohexane furnished white flakes, m.p. 68-69° having a mild camphoraceous odour; IR: 3250, 2960-2890, 1640, 1600, 1540, 1450, 960, 750, 700; PMR: 1.51-1.62 (*m*, 12H), 2.75-2.91 (*m*, 1H), 7.11-7.67 (*m*, 5H), 8.98 (*br*, 1H exchangeable with D_2O) (Found C, 78.2; H, 8.1; N, 6.0. $C_{15}H_{19}NO$ requires C, 78.6; H, 8.3; N, 6.1%).

It was observed that the reaction time of 40 hr provided the maximum yield of **11** (70%) beyond which the yield did not improve. On the otherhand when the refluxing was continued for longer period (optimum 80 hr) only the oxime(**12**) was isolated in 85% yield. **12** was purified by passing through an alumina column. Elution with benzene removed the ketone(**2**) while elution with ethyl acetate provided **12** which recrystallised from clcylohexane, m.p. 135°; IR: 3300-3260, 2980-2880, 1660, 1600, 1550, 1440, 950, 760, 700; PMR: 1.5-1.65 (*m*, 12H), 2.75-2.9 (*m*, 1H), 7.11-7.5 (*m*, 5H), 8.95 (*br*, 1H exchangeable with D_2O) (Found C, 78.1; H, 8.2; N, 6.0. $C_{15}H_{19}NO$ requries C, 78.6; H, 8.3; N, 6.1%).

Beckman reaction of **12**: *Formation of cis-bicyclo*[3.3.0]*-oct-1-anilide*(*N-phenyl-cis-bicyclo*[3.3.0]*oct-1-amide*) (**9**):

(*i*) *In polyphosphoric acid* (*PPA*)[6]

A mixture of **12** (1 g) and PPA (20 g) was stirred for 10 hr at 25°, poured into ice-water (250 ml) with stirring and extracted with ether. The ether layer was washed with brine, dried ($MgSO_4$) and treated with charcoal. Concentration of the ether extract left a semisolid mass which was chromatographed on alumina. Elution with pet-ether (40-60°) afforded unreacted **12** (0.25 g) (25%), m.p. and m.m.p. 135°. Further elution with benzene-ethyl acetate (1:1) furnished **9** (0.55 g) (55%) as a white solid which recrystallised from cyclohexane, m.p. 145-46°; IR: 3460, 2980, 1675, 1600, 1550, 1460, 760; PMR: 1.61-1.72 (*m*, 13H, pentalane), 6.9-7.3 (*m*, 5H, ArH), 7.85 (*br*, 1H, NH) (Found C, 77.9; H, 8.1; N, 6.3. $C_{15}H_{19}NO$ requires C, 78.6; H, 8.3; N, 6.1%).

The foregoing experiment was also carried by varying the reaction conditions and the results are given in Table 1.

(*ii*) *In conc. sulphuric acid*[6]

The oxime (12; 0.5 g) was stirred in conc. H_2SO_4 (5 ml) at room temperature, allowed to stand overnight, diluted with ice-water (50 ml), extracted with ether, organic extract washed with brine and dried ($MgSO_4$). Removal of solvent left a residue which was chromatographed over a column of alumina giving the unchanged **12** (30%) and **9** (60%), identical in all respects (m.m.p., co-TLC, IR) with that obtained by method (i) and (ii) above.

Following the procedure of Fox and Reboulet, the oxime(**12**) was also reacted with 85% H_2SO_4 at 110° for 15 min. The results are given in Table 1.

(iii) *In formic acid* (98-100%)[21]

A mixture of **12** (0.5 g) and HCO_2H (10 ml) was refluxed in an oil-bath at 140° for 6 hr. After removing formic acid the product was diluted with ice-water (50 ml) and extracted with ether. The ether extract was washed with 5% $NaHCO_3$, brine, dried ($MgSO_4$) and solvent removed. The residue was passed through an

alumina column. Elution with pet-ether (40-60°) gave the unchanged **12** (20%). Further elution with benzene-ethyl acetate (1:1) yielded the anilide (**9**) (70%), identical (m.m.p., co-TLC, IR) with that obtained by methods (i) and (ii) above.

(iv) *In phosphorus pentachloride*[6]

A mixture of **12** (0.2 g), PCl_5 (0.6 g) and sodium-dried benzene (6 ml) was stirred (15 hr) at 30°. The reaction mixture was treated with ice-water (50 ml) and extracted with ether. The combined ether extract was washed with 5% aq. Na_2CO_3, brine, dried ($MgSO_4$) and solvent removed. The crude product was chromatographed on an alumina column when elution with pet.ether (40-60°) gave the unreacted **12** (25%). Further elution with benzene-ethyl acetate (1:1) furnished **9** (65%), indistinguishable (m.m.p., co-TLC, IR) from the samples obtained above.

Schmidt reaction of **2**: *Formation of N-cis-1-bicyclo*[3.3.0]*octyl benzamide* (**10**)

Sodium azide (0.065 g) in small portions was added to a mixture of **2** (0.2 g), conc. H_2SO_4 (5 ml) and $CHCl_3$ (20 ml) with stirring at 0-5° during 30 min. Thereafter the mixture was stirred for another 45 min, diluted with ice-water (50 ml) and made alkaline with liquor ammonia. The $CHCl_3$ layer was separated and the aqueous layer repeatedly extracted with $CHCl_3$. The combined chloroform layer was washed with brine, dried ($MgSO_4$) and solvent removed. The crude gummy mass was chromatographed on alumina. Elution with ether furnished **10** (0.12 g, 56%) as the sole isolable product, which recrystallised from cyclohexane giving the TLC pure **10**, m.p. 119°; IR: 3310-3090, 2920, 1670, 1590, 1450, 700; PMR: 1.52-1.66 (*m*, 13H, pentalane), 7.1-7.45 (*m*, 5H, ArH), 7.75 (*br*, 1H, NH) (Found C, 78.2; H, 8.3; N, 6.1. $C_{15}H_{19}NO$ requires C, 78.6; H, 8.3; N, 6.1%).

Preparation of authentic **10**

1-Amino-*cis*-bicyclo[3.3.0]octane (**8**) was prepared as outlined by us[15] and benzoylated according to the following procedure:

To a solution of **8** (0.5 g) in dry pyridine (5 ml) and sodium-dried benzene (10 ml) was added benzoyl chloride (0.5 ml) dropwise and heated on a water-bath at 60-70° for 30 min. The reaction mixture was diluted with water (100 ml) and extracted with benzene. The benzene extract was washed with water, dil. HCl, 5% Na_2CO_3, brine, dried ($MgSO_4$) and solvent removed to afford **10** (0.55 g), which recrystallised from cyclohexane, m.p. 119°, identical (m.m.p., co-TLC, IR) with the product (**10**) obtained from the Schmidt reaction of **2**.

Preparation of authentic **9**

To a solution of the acid chloride (0.85 g) of **1** in benzene (5 ml) was added freshly distilled aniline (0.7 g) in benzene (8 ml). The reaction mixture was warmed on a water-bath for 20 min, cooled, diluted with ice-water (30 ml) and extracted with ether. The ether extract was washed with 10% HCl followed by 5% aq Na_2CO_3, brine, dried ($MgSO_4$) and solvent removed. The residue (0.8 g) was recrystallised from cyclohexane to furnish **9**, m.p. 146° identical (m.m.p., co-TLC, IR) with the product obtained from the Beckmann reaction of the oxime (**12**).

Acknowledgement

The authors thank Dr (Mrs) Alaka Rao, for helpful discussions. The award of a research associateship (to S B) by the UGC, New Delhi, is gratefully acknowledged.

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A Novel Synthesis of Benzopyrano[3,4-*c*]pyrroles & Benzopyrano[4,3-*c*]pyridines—Intramolecular Cyclisation of *o*-Cyanocarbonyl Compounds

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A novel synthesis of benzopyrano[3,4-*c*]pyrrole and benzopyrano[4,3-*c*]pyridine derivatives through the oxidative cyanation of 3-substituted coumarin derivatives and subsequent intramolecular cyclisation of the resulting cyanated products is described.

In an earlier communication[1] we have reported a novel synthesis of benzopyrano[4,3-*b*]pyrrole/pyridine derivative from 4-hydroxycoumarin. The present paper reports a novel synthesis of benzopyrano[3,4-*c*]pyrroles and benzopyrano[4,3-*c*]pyridines through the nitrilation of coumarin nucleus.

Moeckli[2] reported the synthesis of some 4-cyanocoumarin dyes substituted at 3-position with benzazole or cyano group. Hence it was of interest to study the effect of cyanation on the fluorescence properties of the coumarin and to synthesise various fused heterocycles from these cyanated products.

Benzopyrano[3,4-*c*]*pyrrole derivatives* (*Scheme* 1)

Condensation of diethyl acetonedicarboxylate (**2**) with 4-diethylaminosalicylaldehyde (**1a**) in ethanol in the presence of piperidine resulted in 3-(ω-carboethoxyacetyl)-7-diethylaminocoumarin (**3a**)[3]. Compound (**3a**) on cyanation with sodium cyanide in dimethylformamide followed by oxidation with bromine gave a product, the elemental analyses and spectral data of which was consistent with the structure (**7a**) and not **4a**. Its IR spectrum exhibited νNH at 3260 cm^{-1}, its mass spectrum gave the molecular ion peak at *m/z* 356 and its PMR spectrum in $CDCl_3$ displayed the following characteristic signals: δ 1.25 (*t*, 9H, $3\times CH_3$), 3.5 (*q*, 4H, $2\times NCH_2$), 4.2 (*q*, 2H, $-OCH_2$), 6.3-7.3 (*bm*, 5H, 3BrH, 1 olefinic and 1 NH protons). The sharp singlet which appeared in the PMR spectrum of **3a** at δ 8.3 (proton at C-4) distinctly was not seen in that of **7a**.

It is known that cyanoketones undergo intramolecular cyclisation[4] under acidic conditions. The formation of cyclic product (**7a**) can be rationalised on the basis of addition of hydrogen bromide (formed during the reaction) to the cyano group of **4a** to give **5a** followed by an intramolecular cyclisation on the adjacent carbonyl function to give the bromopyrolecoumarin derivative (**6a**). The latter undergoes spontaneous hydrolysis to yield the observed product. The compound (**7a**) was red in colour and was evaluated on polyester.

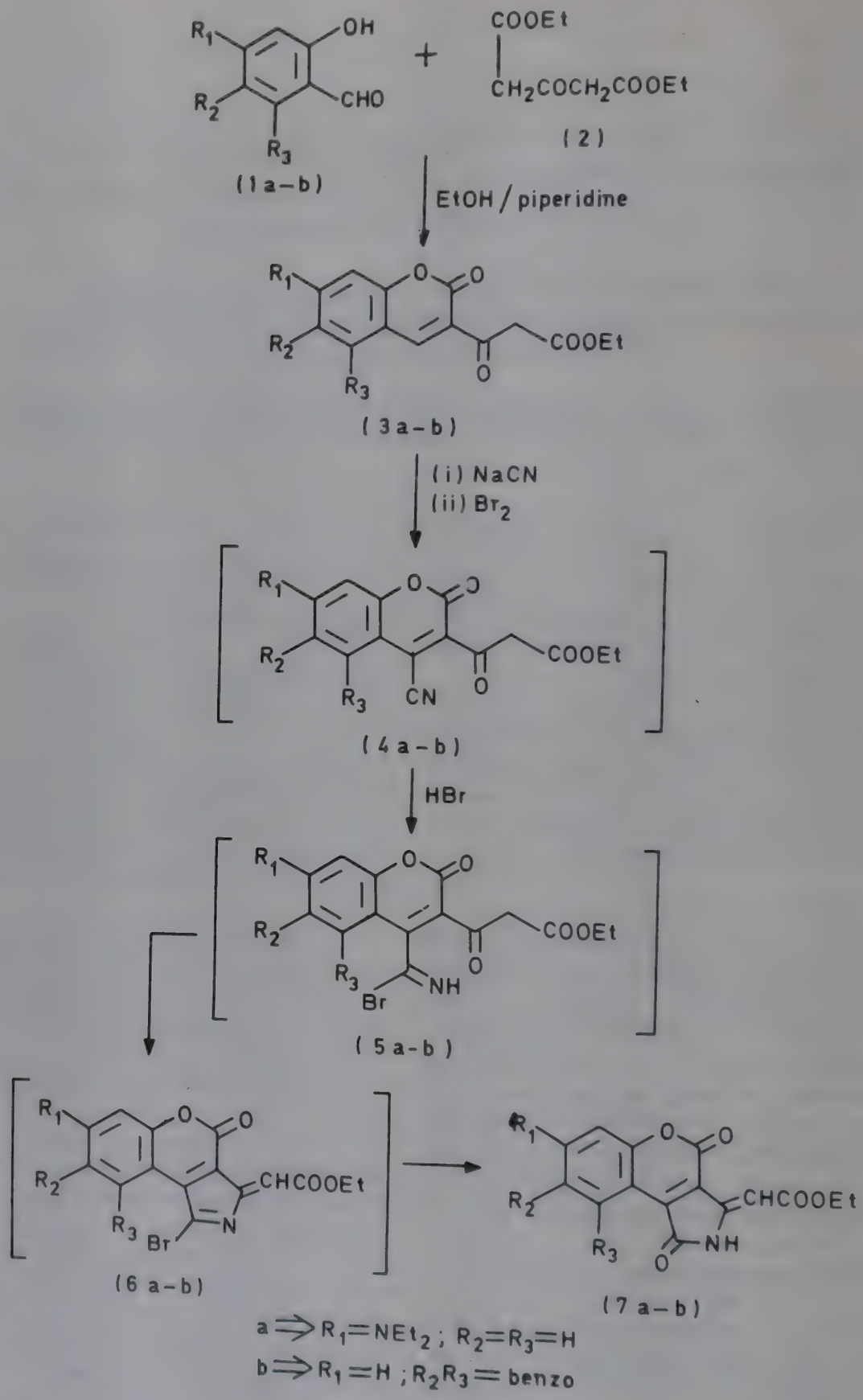
Similarly, 3-(ω-carboethoxyacetyl)-5,6-benzocoumarin (**3b**)[5] underwent a concomittant cyclisation under cyanation conditions to give **7b**. The structure of **7b** was established on the basis of elemental analyses and PMR spectrum in TFA [δ 1.5 (*t*, 3H, CH_3), 4.5 (*q*, 2H, $-CH_2-$), 6.7-8.3 (*bm*, 7H, six aromatic and one olefinic protons)]. The compound (**7b**) showed strong green fluorescence in daylight.

Benzopyrane[,4,3-*c*]*pyridine derivatives* (**10a**,**b**) (*Scheme* 2)

3-Acetylcoumarins (**8a-c**) were cyanated to give 3-acetyl-4-cyanocoumarins (**9a-c**). The structures of **9a-c** were established on the basis of elemental analyses and spectral data. The IR spectra of **9a-c** did not exhibit νC ≡N at 2200 cm^{-1}, attributable to the presence of electron withdrawing keto group adjacent to the cyano group. Absence of cyano peak in certain compounds with electron withdrawing groups in conjugation with the cyano group has been reported by Nakanishi[6] and Bellamy[7]. As a representative PMR spectrum of **9c** was recorded in DMSO-d_6. It displayed the following characteristic signals: δ 1.2 (*t*, 6H, $2\times CH_3$), 2.6 (*s*, 3H, $COCH_3$), 3.5 (*q*, 4H, $2\times CH_2$), 6.9-8.3 (*m*, 3H, aromatic protons). The mass spectrum of **9b** showed the molecular ion peak (M^+) at *m/z* 263 corresponding to the molecular formula $C_{16}H_9NO_3$.

It was anticipated that cyclisation between the cyano and acetyl functions in **9a-c** lead to a novel synthesis of 3,4-heterocyclic fused coumarins. Various, 3,4-heterocyclic fused coumarins synthesised using nucleophiles such as aniline, phenylhydrazine, guanidine, etc. have already been reported[8].

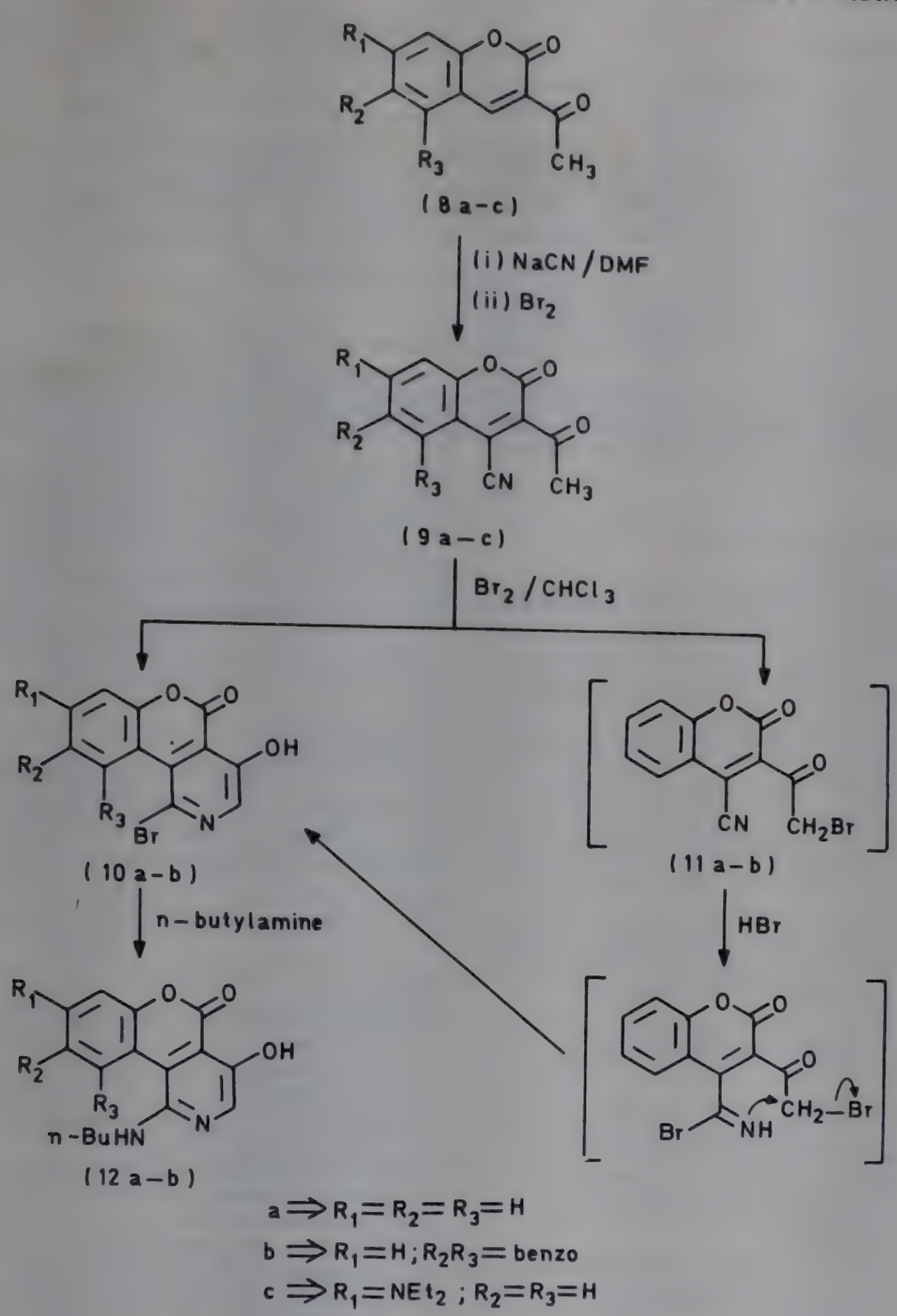
Bromination of 3-acetyl-4-cyanocoumarins (**9a**,**b**) in chloroform resulted in the isolation of cyclic products



SCHEME 1

(**10a,b**) and not **11a,b** The structure of **10a,b** was established on the basis of their chemical properties (solubility in dilute alkali and dilute acid), elemental analyses, spectral data and further reaction (see below). PMR of **10a** in TFA showed only a multiplet in the aromatic region between δ 7.5 and 8.8 (no aliphatic protons) as would be expected for the structure **11a**). and mass spectrum of **10a** showed the molecular ion peak at *m/z* 291 and 293 corresponding to the molecular formula $C_{12}H_6BrNO_3$. These compounds did not fluoresce in daylight.

Reaction of **10a,b** with *n*-butylamine in ethyl alcoh



SCHEME 2

resulted in the formation of the aminated products (**12a,b**), which gave satisfactory elemental analyses. Because of poor solubility and possibly due to the protonation of the NH function a neat PMR spectrum of **12a** would not be obtained in TFA. However, the ratio of the aliphatic to aromatic protons was as expected for structure (**12a**). These compounds showed weak green fluorescence in daylight.

The formation of six-membered ring during the bromination of cyanoketones (**10a,b**) as against the formation of a five-membered ring in case of ketoesters (**3a,b**) is interesting and deserves comment. This difference in behaviour is due to the fact that in the intermediate **11a,b**, the HBr addition product is able to effect a facile intramolecular attack on the neighbouring bromoacetyl function (Scheme 2). Such a possibility does not exist in the case of the intermediates **5a,b** (Scheme 1) wherein intramolecular cyclisation can occur only on the adjacent carbonyl function to give a five-membered ring.

Experimental Procedure

All melting points are uncorrected. UV spectra were recorded in methanol on Beckmann DK-2 and Unicam SP 8000 spectrophotometers, IR spectra in nujol on a Perkin-Elmer 397 spectrophotometer, PMR spectra on a Varian EM-360L spectrometer using TMS as the internal standard and the mass spectra on a Varian Mat CH 7 spectrometer.

Diethyl acetonedicarboxylate (**2**)[9], 4-diethylamino-salicylaldehyde (**1a**)[10], 2-hydroxynaphthaldehyde (**1b**)[11], 3-(ω-carboethoxyacetyl)-7-diethyl-aminocoumarin (**3a**)[3], 3-ω-carboethoxyacetyl)-5,6-benzocoumarin (**3b**)[5], 3-acetylcoumarins (**8a**[12], **8b**[13] and **8c**[14]), m.p. 156-57° were prepared by the reported procedures.

General procedure for cyanation of 3-substituted coumarins

To a solution of 3-substituted coumarin derivative (0.05 mol) in DMF (8-10 ml) at room temperature NaCN (0.1 mol) was added under stirring. After further stirring for 1 hr a clear dark solution was obtained in most cases. The reaction mixture was cooled in an ice-bath to 0.5° and Br_2 (0.055 ml) was added dropwise. The reaction mixture was stirred for 1 hr at room temperature and poured slowly into ice water under vigorous stirring. The product separated was filtered, washed with water and dried. Their characterisation data are as follows:

7a: yield 91%; m.p. 188-91° (EtOH/DMF) (Found: C, 63.6; H, 5.8; N, 7.6. $C_{19}H_{20}N_2O_5$ requires C, 64.0; H, 5.6; N, 7.9%); UV-visible: 510 nm (log ε 4.49).

7b: yield 85%; m.p. 248-50° (C_6H_6) (Found: C, 68.3; H, 4.1; N, 4.5. $C_{19}H_{13}NO_5$ requires C, 68.0; H, 3.9; N, 4.2%).

9a: yield 76%; m.p. 147-49° (EtOH) (Found: N, 6.8. $C_{12}H_7NO_3$ requires N, 6.5%), UV: 365 nm (log ε 2.78).

9b: yield 72%; m.p. 180-83° (EtOH-DMF, 1:1) (Found: N, 5.2. $C_{16}H_9NO_3$ requires N, 5.3%), UV-visible: 401 nm (log ε 3.53).

9c: yield 65%; m.p. 170-72° (EtOH-$CHCl_3$) 1.1 (Found: N, 10.2. $C_{16}H_{16}N_2O_3$ requires N, 9.9%); UV-visible: 490 (log ε 3.95).

Preparation of benzopyrano[4,3-c]pyridines (**10a,b**): *Bromination of 3-acetyl-4-cyanocoumarins* (**9a,b**)

To a solution of 3-acetyl-4-cyanocoumarin (**9a** or **b**) (0.005 mol) in $CHCl_3$ (10 ml), Br_2 (0.005 mol) was added slowly under stirring. The reaction mixture was warmed on a water-bath for 30 min to complete the reaction, cooled, the product obtained filtered off and washed with ether. The product was slurried in dil $NaHCO_3$ solution to remove traces of HBr, filtered, washed with water and dried. Thus **10a** was obtained in 65% yield and was crystallised from HOAc as shining pink crystals m.p. >320°, UV (DMF): 350 nm (4.29) (Found: N, 4.95; Br 27.6. $C_{12}H_6BrNO_3$ requires N, 4.8; Br, 27.1%). Similarly **10b** was obtained in 70% yield and could not be crystallised because of its poor solubility. However, it was repeatedly washed with 1:1 DMF-EtOH; m.p. >300°. Bromination of **9c** however did not given a clean product.

Reaction of **10a,b** *with n-butylamine*

A mixture of **10a** or **b** (0.001 mol) and *n*-butylamine (0.002 mol) was refluxed in ethanol for 2 to 3 hr. The reaction mixture was cooled to room temperature, the solid obtained filtered off, washed with little ethanol and dried. Thus **12a** was obtained in 80% yield and was crystallised from DMF as bright yellow fluffy solid, m.p. 298-300° (Found: N, 10.1. $C_{16}H_{16}N_2O_3$ requires N, 9.9%). Similarly **12b** was obtained in 80% yield and was crystallised from DMF as dull yellow solid, m.p. 243-45°; UV: 480 (log ε 4.47), 450 nm (4.39) (Found: N, 8.8. $C_{20}H_{18}N_2O_3$ requires N, 8.4%).

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Stereoselective Synthesis of Monocyclic β-Lactams from the Reaction of Acid Chlorides/Mixed Anhydrides with Substituted Imines

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Monocyclic β-lactams (IIa-f, IIIa, d) having the desired stereochemistry can be prepared from appropriate imines (Ia-f) on treatment with acid chlorides or mixed anhydrides in the presence of Et_3N. These β-lactams are obtained in appreciable yields and also show some antimicrobial activity.

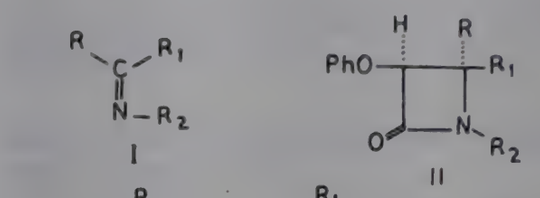
The most important feature of the penicillin and cephalosporin structures is the β-lactam ring, whose synthesis in itself is a challenge. Among the various methods[1-5] available for the synthesis of β-lactams, the one that has received considerable attention is the acid chloride-imine reaction[6,7].

Recently, we have developed[8] a more convenient method through the direct use of acids, involving the use of $POCl_3$ for the annelation of imines to get β-lactams in high yields. An application of this technique was demonstrated later by us[9] for the preparation of α-vinyl-amino-β-lactams through the reaction of potassium carbethoxyacetonylglycinate[10] with schiff bases.

Employing the "acid chloride-imine" and/or "acid imine-$POCl_3$" methods, a number of monocyclic β-lactams (II and III) have been prepared in the present investigation in order to study their stereochemistry and antibacterial potential. In a recent review[11] on β-lactam antibiotic it has been concluded that the bicyclic β-lactam antibiotics do not exhibit exceptional chemical reactivity or reaction mechanisms. Monocyclic β-lactams with suitable electron-withdrawing substituents may be as reactive as bicyclic lactams.

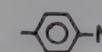
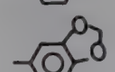
The required aldimines/ketimines (Ia-f) were prepared by the reaction of equimolar quantities of aldehyde/ketone and the corresponding amines using catalytic amount of PTS in anhyd. benzene.

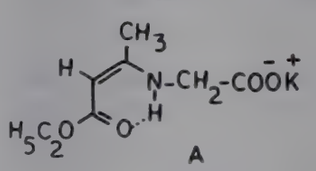
The PMR data of the final products (II, III; Table 1) reveal that mostly *cis*-β-lactams are formed by both the methods (J = 4-6 Hz for the protons at C_3- and C_4-). In the synthesis of monocyclic β-lactams through the annelation of imines, both *cis*- and *trans*-isomers are usually obtained[12]. The stereochemistry depends very much on the nature of the imine used and sometimes one gets only *cis*-β-lactam[8]. The suggestion of Sheehan and Ryan[6] that the formation of a ketene from the acid chloride and tertiary amine and subsequent cycloaddition of the ketone (IV) to the imine (V) is probably not the pathway to β-lactam formation,



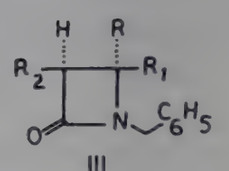
I

II

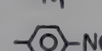
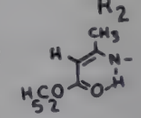
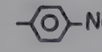
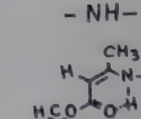
	R	R_1	R_2
(a)	H		$-CH_2C_6H_5$
(b)	H		$-C_6H_5$
(c)	H		-NAPHTHYL
(d)			$-CH_2C_6H_5$
(e)	H		$-CH_2CH_2OH$
(f)			$-CH_2CH_2OH$



A



III

	R	R_1	R_2
(a)	H		
(b)	H		$-NH_2$
(c)	H		$-NH-\overset{O}{\overset{\|}{C}}-CH_2-OPh$
(d)			
(e)			$-NH_2$
(f)			$-NH-\overset{O}{\overset{\|}{C}}-CH_2-OPh$

seems true. Such a cycloaddition should yield the more stable *trans*-isomer (VI).

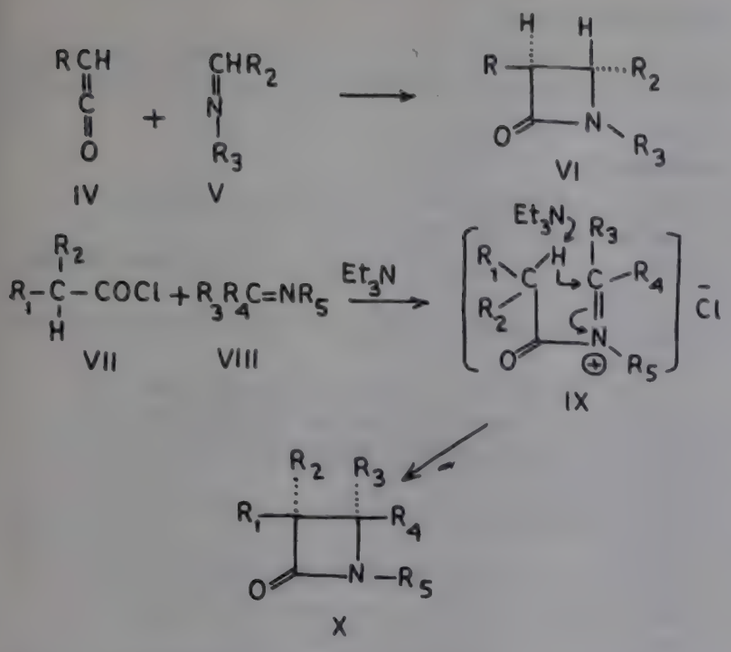
One alternative to the ketene pathway[13,14] involves the addition of acid chloride (VII) to the imine (VIII) to produce a reactive intermediate (IX) which undergoes

Table 1—Characterisation Data of Various β-Lactams Prepared

Compd	m.p. °C	Yield (%)	Mol. formula	Found (%) (Calc.)			Spectral data
				C	H	N	
IIa	162-64	58	$C_{22}H_{18}N_2O_4$	70.4 (70.6)	4.8 (4.9)	7.3 (7.5)	IR: 1760 (β-lactam CO). PMR: 4.1 and 4.93 (*d* each, 1H each, J=15 Hz), 4.98 (*d*, 1H, J=5.5 Hz, C_4-H), 5.6 (*d*, 1H, J=5.5 Hz, C_3-H), 6.8-7.45 (*m*, 10H, Ar−*H*) and 7.55 and 8.25 (*d* each, 2H each, J=9.0 Hz, Ar−*H*).
IIb	155-57	55	$C_{21}H_{16}N_2O_4$	70.2 (70.0)	4.4 (4.5)	7.7 (7.8)	IR: 1755 (β-lactam CO). PMR: 5.5 (*d*, 1H, J=5.0 Hz, C_4-H), 5.65 (*d*, 1H, J=5.0 Hz, C_3-H), 6.8-7.3 (*m*, 10H, Ar−*H*) and 7.55-8.2 (*d* each, 2H each, J=9.0 Hz, Ar−*H*).
IIc	170-72	50	$C_{25}H_{18}N_2O_4$	72.9 (73.2)	4.1 (4.5)	6.3 (6.8)	IR: 1750 (β-lactam CO). PMR: 5.35 (*d*, 1H, J=2.5 Hz, C_4-H), 5.6 (*d*, 1H, J=2.5 Hz, C_3-H) and 7.0-8.2 (*m*, 16H, Ar−*H*).
IId	121-22	70	$C_{27}H_{23}NO_2$	82.6 (82.4)	5.7 (5.9)	3.5 (3.6)	IR: 1760 (β-lactam CO). PMR: 4.2 and 4.5 (*d* each, 1H each, J=15 Hz, $-NCH_2-$), 6.7 (*s*, 1H, C_3-H) and 6.9-7.5 (*m*, 20H, Ar−*H*).
IIe	158-59	70	$C_{18}H_{17}NO_5$	65.8 (66.0)	5.0 (5.2)	4.0 (4.3)	IR: 1770 (β-lactam CO). PMR: 1.8 (*br*, 1H, −OH, exchangeable with D_2O), 2.95-4.0 (*m*, 4H, $-NHC_2-$ and $-OCH_2-$), 5.1 (*d*, 1H, C_4-H), 5.55 (*d*, 1H, C_3-H) 6.05 (*s*, 2H, $-OCH_2O-$) and 6.8-7.45 (*m*, 8H, Ar−*H*).
IIf	82-83	65	$C_{23}H_{21}NO_3$	76.7 (76.9)	5.7 (5.8)	3.7 (3.9)	IR: 1760 (β-lactam CO). PMR: 3.0-3.6 (*m*, 2H, $-NCH_2-$), 3.7-4.5 (*m*, 2H, 1H, $-OCH_2-$ & −OH, exchangeable with D_2O), 5.85 (*s*, 1H, C_3-H) and 6.8-7.7 (*m*, 15H, Ar−*H*).
IIIa	73-75	63	$C_{22}H_{23}N_3O_5$	64.4 (64.6)	5.5 (5.6)	10.1 (10.3)	IR: 1750 (β-lactam CO) and 1640 (conjugated ester CO).
IIIb	Oil	50	$C_{16}H_{15}N_3O_3$	64.3 (64.6)	5.0 (5.1)	14.4 (14.1)	IR: 3350 & 3300 ($-NH_2$) and 1750 (β-lactam CO). PMR: 2.1 (*br*, 2H, $-NH_2$), 4.1 and 4.5 (*d* each, 1H each, J=15 Hz, $-NCH_2-$), 4.8 (*d*, 1H, J=5.5 Hz, C_4-H), 5.0 (*d*, 1H, J=5.5 Hz, C_3-H), 7.4 (*br s*, 5H, $-C_6H_5$) and 8.2 & 8.5 (*d* each, 2H each, J=9.0 Hz, Ar−*H*).
IIIc	128-30	50	$C_{24}H_{21}N_3O_5$	66.4 (66.8)	4.5 (4.9)	9.5 (9.7)	IR: 3250 (−N−H), 1760 (β-lactam CO) and 1670 (amide CO). PMR: 4.0-4.7 (complex pattern, 4H, $-NHC_2-$ and $-COCH_2-$), 5.1 (*d*, 1H, J=5.5 Hz, C_4-H), 5.5 (*dd*, 1H, J=5.5 Hz and 9.0 Hz, C_3-H), 6.8-7.4 (*m*, 10H, Ar−*H*), 7.4 and 8.0 (*d* each, 2H each, J=9.0 Hz, Ar−*H*) and 8.2 (*d*, 1H, J=9.0 Hz, −NH).
IIId	122-14	63	$C_{28}H_{28}N_2O_3$	76.0 (76.3)	6.3 (6.4)	6.7 (6.4)	IR: 1745 (β-lactam CO) and 1640 (conjugated ester CO). PMR: 1.15 (*t*, 3H, $-CO-OCH_2CH_3$), 1.95 (*s*, 3H, allylic $-CH_3$), 3.95 (*q*, 2H, $-CO-OCH_2CH_3$), 4.4 (*s*, 1H, olefinic H), 4.25 and 4.65 (*d* each, 1H each, J=15 Hz, $-NCH_2$), 5.5 (*d*, 1H, J=9.0 Hz, C_3-H), 7.25 and 7.4 (*s*, 15H, Ar−*H*) and 8.5 (*d*, 1H, J=9.0 Hz, −NH).
IIIe	40-42	55	$C_{22}H_{20}N_2O$	80.1 (80.5)	6.1 (6.2)	8.2 (8.5)	IR: 3380 and 3275 ($-NH_2$) and 1750 (β-lactam CO). PMR: 1.2 (*s*, 2H, $-NH_2$), 4.15 and 4.45 (*d* each, 1H each, J=15 Hz, $-NCH_2$), 4.75 (*s*, 1H, C_3-H) and 7.15-7.3 (*s*, 15H, Ar−*H*).
IIIf	168-70	52	$C_{30}H_{26}N_2O_3$	77.6 (77.9)	5.6 (5.7)	6.3 (6.1)	IR: 3230 (N−H), 1755 (β-lactam CO) and 1650 (amide CO).

cyclisation to a β-lactam (X) under the influence of the tertiary base. Exclusive formation of the less stable *cis*-β-lactams in many instances is not easily explainable. Such an exclusive formation of a single isomer is also observed in the synthesis of bicyclic β-lactams[15,16] from many cyclic imines.

Another noteworthy feature in the PMR spectrum of the monocyclic β-lactams (II and III) is the



appearance of the $-NCH_2-$ protons. These are non-equivalent and each one appears as a doublet with a large coupling constant (J=15-16 Hz). It can be attributed to the dissymmetry imparted to these β-lactams by the nitrogen atom.

That, this could also be due to the achiral centre at C-4 was proved untrue by a PMR study of the β-lactams (IId, f, IIId-f) formed by the annelation of schiff bases (Id and If). Even in the absence of a chiral centre at C-4, the PMR spectra of these β-lactams exhibited the $-N-CH_2-$ signals as a pair of doublets with a large coupling constant.

Biological activity

The *in vitro* antibacterial screening of some of the β-lactams reported here against a number of gram positive as well as gram negative bacteria indicated that these compounds do have some antibacterial activity at 600 μg/ml concentration.

Experimental Procedure

All melting points reported are uncorrected. IR spectra (ν_{max} in cm^{-1}) were recorded in nujol mull on a Perkin-Elmer 337 spectrophotometer, and PMR spectra in $CDCl_3$ on a Varian EM-390 90 MHz instrument using TMS as internal standard (chemical shifts in δ, ppm). Organic extracts were dried over anhyd. sodium sulphate.

Schiff bases (Ia-f): General method

These were prepared by refluxing a benzene solution of equimolar quantities of the appropriate primary amine and aromatic aldehyde/ketone in the presence of a catalytic amount of PTS using a Dean-Stark water separator. After removing the solvent, the residue was recrystallised from ethanol. The schiff bases thus prepared were characterised by their satisfactory spectroscopic data.

1-Benzyl-4-p-nitrophenyl-3-phenoxyazetidin-2-one (IIa)

Phenoxyacetyl chloride (1.71 g, 0.01 mol) in dry dichloromethane (100 ml) was added dropwise to a well stirred mixture of the imine Ia (2.40 g, 0.01 mol) and triethylamine (1.01 g, 0.01 mol) in dry dichloromethane (75 ml) at 5-10°. After the completion of addition, the reaction mixture was stirred overnight at room temperature. The resulting mixture was washed successively with water, 5% $NaHCO_3$ (aq.), 5% HCl (aq.) and again with water and dried. Removal of solvent afforded the desired compound which was recrystallised from ethanol.

The β-lactams IIb-d were prepared by the reaction of the imines Ib-d with phenoxyacetyl chloride in a similar manner as described for the preparation of IIa. Their characterization data are given in Table 1.

N-(β-Hydroxyethyl)-4-methylenedioxyphenyl-3-phenoxyazetidin-2-one (IIe)

Trimethylsilyl chloride (1.09 g, 0.01 mol) in dry CH_2Cl_2 (150 ml) was added dropwise to a well stirred mixture of the imine Ie (1.93 g, 0.01 mol) and triethylamine (2.02 g, 0.02 mol) in anhyd. dichloromethane (75 ml) at 5-10°. After stirring for 30 min, phenoxyacetyl chloride (1.71 g, 0.01 mol) in dry CH_2Cl_2 (100 ml) was added dropwise to the above mixture and the reaction mixture stirred overnight. Thereafter, it was stirred with a mixture of water and methanol (10 ml) for half an hr, washed with water and dried. Removal of solvent afforded the title compound which was recrystallised from ethanol. The β-lactam IIf was also prepared in a similar manner using the imine If. The characterisation data of these compounds are given in Table 1.

1-Benzyl-3-carbethoxyacetonylamino-4-p-nitrophenylazetidin-2-one (IIIa)

The schiff base Ia (2.40 g, 0.01 mol), potassium carbethoxyacetonylglycinate (A; 2.25 g, 0.01 mol) and triethylamine (2.02 g, 0.02 mol) were stirred in dry dichloromethane (150 ml) at 5-10°, while a solution of $POCl_3$ (1.54 g, 0.01 mol) in dry CH_2Cl_2 (75 ml) was added to it dropwise during half an hr. After the addition was over, the mixture was stirred for 4 hr and then refluxed for 1 hr. The resulting solution was washed with brine, dried, and solvent removed to afford the desired compound IIIa. Compound IIId was similarly prepared from the imine Id in a good yield (Table 1).

3-Amino-1-benzyl-4-p-nitrophenylazetidin-2-one (IIIb)

The enamino-β-lactam IIIa (1.9 g) was stirred in a solution of ethanol (20 ml) and conc. HCl (10 ml) for

4 hr at room temperature. After stirring, the reaction mixture was diluted with water and extracted with dichloromethane (3 × 50 ml) to remove any unreacted material. The aq. solution was made alkaline with Na_2CO_3 (solid) and extracted with dichloromethane (3 × 50 ml). The organic layer was washed with water, dried, and solvent removed to provide the title compound in pure state. Compound IIIe was similarly prepared from IIId. The characterization data of these β-lactams are given in Table 1.

1-Benzyl-4-p-nitrophenyl-3-phenoxyacetamidoazetidin-2-one (IIIc)

Phenoxyacetyl chloride (1.71 g, 0.01 mol) in dry CH_2Cl_2 (100 ml) was added dropwise to a well stirred solution of IIIb (2.97 g, 0.01 mol) and triethylamine (1.01 g, 0.01 mol) in dry CH_2Cl_2 (100 ml) at 5-10°. After the addition was over, the solution was stirred further for 4-5 hr at room temperature. The resulting solution was washed with water, dried, and solvent removed to afford the desired compound IIIc which recrystallised from ethanol. A similar reaction of IIIe provided IIIf (Table 1).

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Synthesis of Nitriles from Haloesters, Haloketones & Haloethers†

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The action of NaCN on haloesters, haloketones and haloethers has been studied. Haloesters wherein halogen and ester functions are located on adjacent carbon atoms, do not furnish the corresponding nitriles, whereas those with halogen and ester functions not located on adjacent carbon atoms, furnish the corresponding nitriles in good yields. The presence of hydroxy or ether function on the carbon adjacent to primary halide bearing carbon atom does not interfere in the reaction with cyanide. δ-Haloketones are transformed to ketonitriles, γ-Haloketones are transformed to cyclopropyl ketones and epoxyhalides to epoxynitriles.

In connection with the synthesis of 2-deoxyerythropentose (deoxyribose) and other aldehydes[1-3], we examined the transformations of halides containing other functional groups, such as haloesters, haloketones and haloethers, to nitriles under different conditions. The results of this investigation which proved useful in planning the synthesis of deoxyribose are presented in this paper.

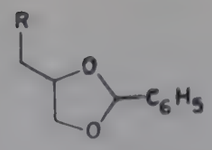
There are several reports on the transformation of alkyl halides to nitriles and this reaction has been reviewed[4,5]. The reaction proceeds to give the nitriles in good yield when dimethyl sulphoxide or N-methylpyrrolidone[6] is used as solvent; it can also be carried out in a two-phase system[7] with a phase transfer catalyst. Before studying the reaction of complex halides we examined the reaction of NaCN as well as KCN on *n*-octyl bromide and *n*-octyl chloride. Since better yields were obtained with NaCN, it was preferred over KCN for further studies.

The haloester (**6**) failed to furnish the corresponding nitrile under the following experimental conditions: (a) in DMSO at 65 /2 hr; (b) in DMSO at 110 /10 min; (c) in DMSO at 25 /24 hr; and (d) in a two-phase system with tetra-*n*-pyropylammonium bromide as phase transfer catalyst. The haloesters (**7**, **12**, **18**, **19**, **20**, **24**, **26**) and the acetal (**3**) failed to furnish the corresponding nitriles on reaction with NaCN. The haloesters (**10**, **13**, **33**, **36**, **38**) hydroxyhalides (**8**, **15**, **41**), δ-haloketones (**50**, **64**), epoxy halide (**59**) and ketal halide (**56**) furnished the corresponding nitriles in satisfactory yields. γ-Haloketones (**45**/**62**) furnished with NaCN the cyclopropyl ketones (**53**/**58**). However, the nitriles (**50**/**63**), which could not be prepared directly from the halides (**45**/**62**) were prepared indirectly; BF_3-etherate catalysed rearrangement of **60** furnished **63** and deketalization of **57** furnished **50**.

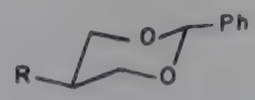
Ziderman[8] has observed that the reaction of the haloester (**22**) with KCN in dimethylformamide does not furnish the corresponding nitrile; the hydroxy compound (**21**) is obtained in low yield. To explain this observation he has suggested that **22** is initially transformed to the 1,3-dioxolan-2-ylium cation (**30**). In the present study the failure to obtain nitriles from haloesters wherein the ester and halogen functions are located on adjacent carbon atoms (e.g. ester **6**) is probably due to the ready formation of 1,3-dioxolan-2-ylium cations[9] related to **30**. It is to be noted that haloesters wherein halogen and ester functions are not located on adjacent carbon atoms (e.g. haloester **13**) furnish the corresponding nitriles in good yields. The presence of hydroxy (e.g. **8**) or ether function on the carbon adjacent to primary halide bearing carbon (e.g. **41**) does not interfere in the reaction with cyanide. Haloketones wherein the carbonyl group is separated from halogen bearing carbon by three or more carbon atoms (e.g.**50**) furnish cyanoketones. A convenient procedure to transform polyhydroxyhalides to the corresponding polyacetoxynitriles (e.g. **8**→**9**) has been developed and details are given in experimental section.

Bromobenzoates have been prepared in good yields by Hanessian[10,11] and others by reacting benzylidene acetals with N-bromosuccinimide (NBS). This reaction has been used for the preparation of haloesters (**6**, **10**, **12**, **13**, **20**, **23**, **33**, **40**) from the appropriate benzylideneacetals. Reaction of 1,3 : 2,4-di-O-benzylideneerythritol with equimolecular quantity of NBS furnished in good yields the haloester (**40**), a key intermediate for the synthesis of 2-deoxyribose. However, this method could not be used for the preparation of haloester (**32**), a potential intermediate

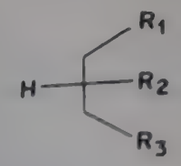
†NCL Communication No. 3778.



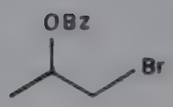
1 R=OH
2 R=OCOC$_6$H$_5$
3 R=Cl



4 R=OH
5 R=OCOC$_6$H$_5$



6 R$_1$=Br ; R$_2$=R$_3$=OCOC$_6$H$_5$
7 R$_1$=Cl ; R$_2$=R$_3$=OAc
8 R$_1$=Cl ; R$_2$=R$_3$=OH
9 R$_1$=CN; R$_2$=R$_3$=OAc
10 R$_1$=Br ; R$_2$=H; R$_3$=OBz
11 R$_1$=CN; R$_2$=H; R$_3$=OBz



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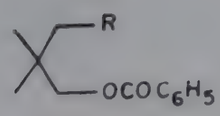
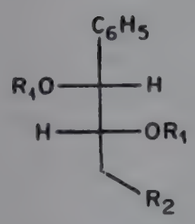
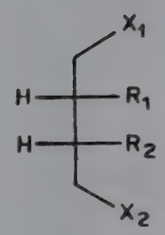


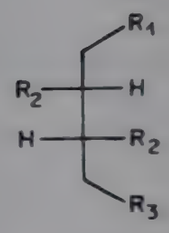
13 R=Br
14 R=CN



15 R$_1$=H , R$_2$=Cl
16 R$_1$=Ac, R$_2$=Cl
17 R$_1$=Ac, R$_2$=CN



18 X$_1$=X$_2$=Cl , R$_1$=R$_2$=OAc
19 X$_1$=X$_2$=Br , R$_1$=R$_2$=OAc
20 X$_1$=X$_2$=Br , R$_1$=R$_2$=OBz
21 X$_1$=X$_2$=R$_2$=OBz , R$_1$=OH
22 X$_1$=Br; R$_1$=R$_2$=X$_2$=OBz



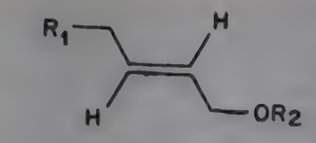
23 R$_1$=R$_3$=Br , R$_2$=OBz
24 R$_1$=Br, R$_2$=R$_3$=OAc
25 R$_1$=Br , R$_2$=OH, R$_3$=OAc
26 R$_1$=Br , R$_2$=R$_3$=OBz
27 R$_1$=Br , R$_2$=OH, R$_3$=OBz

for the synthesis of 2-deoxythreopentose since the action of equimolecular quantity of NBS on 1,3 : 2,4-di-O-benzylidenethreitol furnishes the haloester (**23**). 2-Acetoxybenzoyl chloride[12] has been empolyed for the transformation of glycerol and erythritol to the chloroacetatess (**7**) and (**18**) respectively. 2-Acetoxybenzoyl bromide[13] has been employed for the preparation of the bromoacetate (**19**) from erythritol. The threo-diol (**15**) has earlier been prepared via *cis*-hydroxylation[14] of cinnamyl chloride with catalytic amounts of osmium tetroxide; this method has also been used for the synthesis of hydroxy compounds (**25**/**27**) from the unsaturated compounds (**28**/**29**).

Convenient procedures have been developed for the preparation of several halides required for this investigation and details are given in the experimental section.

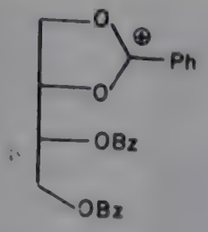
Experimental Procedure

All the compounds reported were characterised by their IR and PMR spectra; spectral data are given only for a few typical compounds. The purity of compounds was checked by TLC; in the case of volatile compounds the purity was checked by GLC. KCN (BDH) was of 96.7% purity while NaCN, a commercial product, was of 92.1% purity. All organic extracts were dried over anhydrous Na_2SO_4. Unless otherwise stated, reactions were carried out in 5-20 mmol scale. 60 MHz PMR spectra were determined in CCl_4 using TMS as an



28 R_1 = Br ; R_2 = Ac

29 R_1 = Br ; R_2 = Bz



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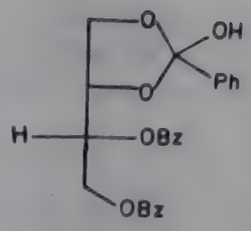

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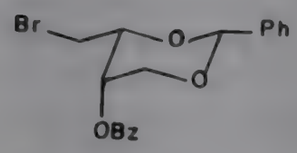

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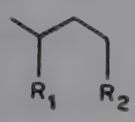
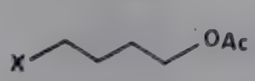


33 R_1=OBz ; R_2=Br

34 R_1=Br ; R_2=OBz

35 R_2=CN ; R_1=OBz

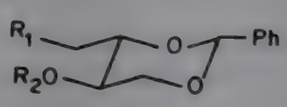


36 X = Cl

37 X = CN

38 X = CH_2CH_2Cl

39 X = CH_2CH_2CN

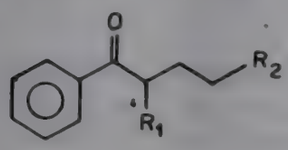


40 R_1=Br ; R_2=Bz

41 R_1=Br ; R_2=H

42 R_1= CN; R_2=H

43 R_1=CN ; R_2= Ac



44 R_1=H ; R_2=CO_2H

45 R_1=H ; R_2=Cl

46 R_1=H ; R_2=CH_2CO_2H

47 R_1=H ; R_2=CH_2Cl

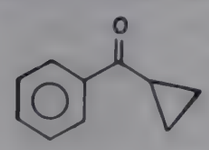
48 R_1=Br ; R_2=CH_2Cl

49 R_1=H ; R_2=CH_2CN

50 R_1=H ; R_2=CN

51 R_1=H ; R_2=CH_2CH_2Br

52 R_1=Br ; R_2=CH_2CH_2Br



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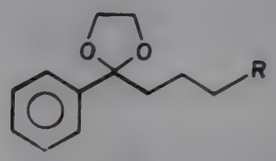
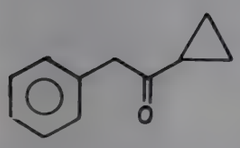


54 R = OH

55 R = OTs

56 R = I

57 R = CN



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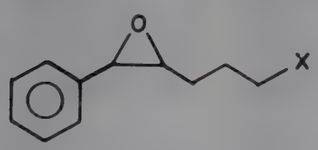
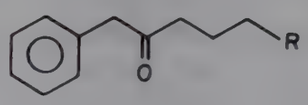


59 X = Cl

60 X = CN

61 X = CH_2Br



62 R = Cl

64 R = CH_2Br

63 R = CN

65 R = CH_2CN

internal standard (chemical shifts in δ ppm). All chiral substances reported in this paper are recemates.

Reaction of 1-bromooctane with sodium cyanide: Method A

A mixture of 1-bromooctane (1 g), DMSO (5 ml) and NaCN (0.5 g) was heated at 100° for 2 hr. The reaction product was isolated in the usual manner and distilled to furnish nonanenitrile (yield 85 %) identified by direct comparison (GLC, PMR) with an authentic sample.

Method B

A mixture of NaCN (1.5 g), water (2.0 ml), benzene (5 ml), 1-bromooctane (2.0 g) and tetra-*n*-propylammonium bromide (0.27 g) was stirred at 60-70° for 4 hr and cooled at 25°C. Water and benzene were added to the reaction mixture, the benzene separated, washed with water, dried and solvent evaporated. Distillation of residue furnished the nonanenitrile (1.32 g, 92 %) (Purity by GLC = 99 %).

Reaction of 1-chlorooctane with sodium cyanide

A mixture of 1-chlorooctane (1.0 g) DMSO (5 ml) and NaCN (0.67 g) was stirred at 25°C for 24 hr. Working-up as in earlier experiments and vacuum distillation furnished nonanenitrile (yield 94%) (Purity by GLC = 99%).

3-*Bromo*-1,2-*dibenzoyloxypropane* (**6**)

A mixture of acetals (**1**/**4**) obtained by reacting glycerol with benzaldehyde was benzoylated with pyridine-benzoyl chloride to give a mixture of benzoates (**2**/**5**). **2**/**5** (2.3 g), N-bromosuccinimide (1.576 g), benzoyl peroxide (0.07 g) and CCl_4 (50 ml), was heated under reflux for 3 hr, filtered and the residue washed with CCl_4. The combined CCl_4 layer was washed with water, dried and the solvent evaporated. Recrystallization of the residue from pet. ether-benzene furnished **6** (2.1 g), yield 71%; m.p. 72-73° (lit.[15] m.p. 75°).

1,2-*Diacetoxy*-3-*chloropropane* (**7**)

A mixture of glycerol (2.02 g), *o*-acetoxybenzoyl chloride (6.55 g) and acetic acid (10 ml) was stirred at 25° for 10 min and then heated at 80° for 2 hr. Acetic acid was distilled *in vacuo*, the residue diluted with water and extracted with ether. The ether extract was washed with aq. sodium carbonate, water, dried and the solvent removed. The residue obtained was distilled under reduced pressure to furnish **7** (2.6 g); yield 61%; b.p. 125° (bath)/10 mm (lit.[16] b.p. 115-16°/10 mm).

3,4-*Diacetoxybutyronitrile* (**9**)

Chlorodiol (**8**, 2.21 g) was added to a mixture of NaCN (2.0 g) and DMSO (10 ml) at 25°. The reaction mixture was stirred at 25° for 24 hr and excess NaCN destroyed by adding methyl iodide (1 ml) at 10°C and stirring at 25° for 24 hr. Subsequently pyridine (5 ml) and acetic anhydride (2 ml) were added. After keeping at 25° for 12 hr, the reaction mixture was diluted with water and extracted with ether. The ether extract was washed with water, dried and the solvent evaporated. Distillation of residue furnished **9** (1.25 g), yield 34%, b.p. 120° (bath)/0.2 mm (lit.[17] b.p. 132-34°/4 mm; IR: 2240 (C≡N), 1740 (C=O); PMR: 2.03 (3H, *s*, CH_3-CO), 2.07 (3H, *s*, CH_3-CO), 2.71 (2H, *d*, $J=6$ Hz, $-CH_2-CN$), 4.17 (2H, *m*, CH_2-O), 5.15 (1H, *m*, $-CH-O$) (Found: C, 51.7; H, 6.1. $C_8H_{11}NO_4$ requires C, 51.9; H, 6.0%).

4-*Benzoyloxybutyronitrile* (**11**)

3-Bromopropyl benzoate (**10**) was prepared in 87% yield by reacting 2-phenyl-1,3-dioxane with NBS. Reaction of **10** with NaCN in DMSO at 60°/2 hr furnished **11** in 82% yield; b.p. 145° (bath)/0.6 mm (Found: C, 69.9; H, 6.0. $C_{11}H_{11}NO_2$ requires C, 69.8; H, 5.9%).

2-*Benzoyloxy*-1-*bromopropane* (**12**)

Reaction of 4-methyl-2-phenyl-1,3-dioxalane with NBS furnished **12** in 82% yield; b.p. 155° (bath)/10 mm (lit.[18] b.p. 104°/0.3 mm).

3-*Bromo*-2,2-*dimethylpropanyl benzoate* (**13**)

5,5-Dimethyl-2-phenyl-1,3-dioxane was reacted with NBS. The product was chromatographed on grade II alumina and the fraction eluted with pet. ether-ethyl acetate (99:1) furnished **13** in 90% yield (Found: C, 52.9; H, 5.3. $C_{12}H_{15}BrO_2$ requires C, 53.1; H, 5.4%).

4-*Benzoyloxy*-3,3-*dimethylbutanenitrile* (**14**)

Reaction of **13** with NaCN in DMSO at 100° for 8 hr furnished **14** in 69% yield. The product was purified through chromatography on a column of alumina and eluting with 97:3 mixture of pet. ether-ethyl acetate (Found: C, 72.0; H, 7.1. $C_{13}H_{15}NO_2$ requires C, 71.9; H, 7.0%).

threo-3-*Chloro*-1-*phenyl*-1,2-*propanediol* (**15**)

Hydroxylation of *trans*-cinnamyl chloride according to the method of Sharpless and Akashi[12,14] furnished **15** in 90% yield. Acetylation (Py/Ac_2O) of **15** gave the diacetate (**16**); b.p. 145° (bath)/0.7 mm; PMR: 2.0 (6H, *s*, CH_3-CO-), 3.33 (2H, 8lines, AB portion of ABX $-CH_2-Cl$) 5.2 (1H, *m*, $-CHOAc$), 5.86 (1H, *d*, $J=7$ Hz, Ar-CH), 7.18 (5H, *s*, aromatic H) (Found: C, 57.7; H, 5.8. $C_{13}H_{15}ClO_4$ requires C, 57.7; H, 5.7%).

threo-3,4-*Diacetoxy*-4-*phenylbutyronitrile* (**17**)

15 was reacted with NaCN, the resulting product acetylated *in situ* as described for **9** and the product chromatographed on a column of grade II alumina. The fraction eluted with 92:8 pet. ether-ethyl acetate furnished **17** in **50** yield; m.p. 92-93° (Found: C, 64.6; H, 5.8; N, 5.2. $C_{14}H_{15}NO_4$ requires C, 64.4; H, 5.8; N, 5.4%).

erythro-2,3-*Diacetoxy*-1,4-*dichlorobutane* (**18**)

Erythritol was reacted with *o*-acetoxybenzoyl chloride according to the procedure given for **7** to furnish **18** in 32% yield; m.p. 117-18° (lit.[19] m.p. 117°).

erythro-2,3-*Diacetoxy*-1,4-*dibromobutane* (**19**)

Erythritol was reacted with *o*-acetoxybenzoyl bromide according to a known procedure[7]. The reaction product was purified through chromatography on grade II alumina; the fraction eluted with 9:1 pet. ether-ethyl acetate afforded **19**; yield 38%, m.p. 138-39° (lit.[20] m.p. 136.5-37°).

erythro-2,3-*Dibenzoyloxy*-1,4-*dibromobutane* (**20**)

Reaction of 1,3:2,4-di-O-benzoylidene erythritol with 2 molar equivalent of NBS according to the procedure described for **6** furnished **20** in 75% yield, m.p. 179-80° (lit.[20] m.p. 183-85°).

threo-2,3-*Dibenzoyloxy*-1,4-*dibromobutane* (**23**)

1,3:2,4-di-O-benzylidenethreitol (1.6 g) was reacted

with molar equivalent of NBS. The reaction product was recrystallized from pet. ether-benzene to give **23** (0.9 g); m.p. 112-13° (Found: C, 47.4; H, 3.6. $C_{18}H_{16}Br_2O_4$ requires C, 47.5; H, 3.5%).

1-*Bromo*-1-*deoxy*-*tri*-*O*-*acetylthreitol* (**24**)

cis-Hydroxylation of **28** (as in the case of **15**) furnished the diol (**25**) in 75% yield which on acetylation (Py/Ac_2O) gave **24** in 70% yield, b.p. 130° (bath)/0.5 mm; PMR: 3.5 (2H, *m*, CH_2-Br), 3.85 (2H, octet, $-CH_2-OAc$), 5.42 (2H, *m*, $CH-OAc$) (Found: C, 38.6; H, 4.6. $C_{10}H_{15}BrO_6$ requires C, 38.6; H, 4.8%).

1-*Bromo*-1-*deoxy*-*tri*-*O*-*benzoylthreitol* (**26**)

cis-Hydroxylation[19] of **29** furnished the diol (**27**) in 79% yield. Benzoylation (Py/BzCl) of **27** gave **26** in 65% yield; PMR: 3.75 (2H, *d*, $J = 6$ Hz, CH_2-Br), 4.71 (2H, *d*, $J = 5$ Hz, $-CH_2-OBz$), 5.95 (2H, *m*, $-CH-O-Bz$) (Found: C, 60.9; H, 4.5 $C_{25}H_{21}BrO_6$ requires C, 60.4; H, 4.2%).

1-*Acetoxy*-4-*bromo*-*but*-2*E*-*ene* (**28**)

Reaction of crotyl acetate with molar equivalent of NBS furnished **28** in 40% yield; b.p. 62°/0.6 mm (lit.[21] b.p. 49°/0.35 mm).

trans-1-*Benzoyloxy*-4-*bromo*-2-*butene* (**29**)

Crotyl benzoate was reacted with molar equivalent of NBS. The product was purified through chromatography on silica gel column. The fraction eluted with 97:3 mixture of pet. ether-ethyl acetate furnished **29** in 40% yield; b.p. 160° (bath)/0.2 mm; PMR: 3.93 (2H, *d*, $J = 8$ Hz; $-CH_2-Br$), 4.8 (2H, *d*, $J = 6$ Hz, $-CH_2-OBz$), 5.85 6.11 (2H, *m*, vinyl H).

3-*Benzoyloxy*-1-*bromobutane* (**33**)

Reaction of 4-methyl-2-phenyl-1,3-dioxane with NBS furnished in 70% yield 4:1 mixture (analysis by PMR) of **33** and **34**; b.p. 134°/3 mm (lit.[22] b.p. 124-25°/2 mm).

4-*Benzoyloxypentanenitrile* (**35**)

A mixture (4:1) of **33** and **34** was reacted with NaCN in DMSO at 95° for 4 hr. The product was purified through chromatography on a column of grade II alumina. Elution with pet. ether-ethyl acetate (96:4) furnished **35** in 69% yield (Found: C, 70.6; H, 6.7; N, 6.9. $C_{12}H_{13}NO_2$ requires C, 70.9; H, 6.5; N, 6.9%).

4-*Cyanobutyl acetate* (**37**)

Reaction of 4-chlorobutyl acetate[23] with NaCN in DMSO at 75° for 2 hr furnished in 90% yield the nitrile **37**, b.p. 140° (bath)/20 mm (Found: C, 59.3; H, 8.0; N, 9.9. $C_7H_{11}NO_2$ requires C, 59.6; H, 7.9; N, 9.9%).

6-*Chlorohexyl acetate* (**38**)

6-Acetoxyhexanol was prepared in 20% yield by saponifying 1,6-diacetoxyhexane with 0.5 molar equivalent of Na_2CO_3 in 4:3 mixture of ethanol and water at 25° for 2.5 hr. Chromatography of the reaction product on grade II alumina using pet. ether-ethyl acetate (9:1) as an eluent furnished the desired 6-acetoxyhexanol.

A mixture of 6-acetoxyhexanol (1.8 g), thionyl chloride (12 ml) and dimethylformamide (1 ml) was heated under reflux for 2 hr. Usual work-up followed by distillation of the residual mass furnished **38** (1.7 g); b.p. 109°/5 mm (lit.[24] b.p. 88-90°/3.4 mm).

6-*Cyanohexyl acetate* (**39**)

Reaction of haloester **38** with NaCN in DMSO at 80° for 2 hr furnished ester **39** in 70% yield; b.p. 120°/0.3 mm (Found: C, 63.7; H, 9.0; N, 8.2. $C_9H_{15}NO_2$ requires C, 63.9; H, 8.9; N, 8.3%).

2,4-*O*-*Benzylidene*-1-*bromo*-1-*deoxyerythritol* (**41**)

A mixture of benzoate[3] (**40**, 2 g), methanolic solution of KOH (5 ml; 10%) and water (10 ml) was heated under reflux. The saponification product was chromatographed on a column of grade II alumina. Elution with pet. ether-ethyl acetate (9:1) furnished **41** (1.12 g); yield 77% (Found: C, 48.4; H, 4.5. $C_{11}H_{13}BrO_3$ requires C, 48.4; H, 4.8%).

4-*O*-*Acetyl*-3,5-*O*-*benzylidene*-2-*deoxyerythro*-*pentanenitrile* (**43**)

41 was reacted with NaCN in DMSO at 25° for 72 hr. The reaction product **42** was acetylated (Py/Ac_2O) and the resulting acetyl derivative chromatographed on grade II alumina. Elution with pet. ether-ethyl acetate (95:5) furnished the nitrile **43** in 69% yield; m.p. 85-86° (Found: C, 64.2; H, 5.7. $C_{14}H_{15}NO_4$ requires C, 64.4; H, 5.8%).

4-*Chloro*-1-*phenylbutan*-1-*one* (**45**)

A mixture of **44** (10 g), benzene (100 ml) and lead tetraacetate (46 g) was stirred at 25° for 1 hr[25]. After adding anhydrous LiCl (4.4 g) the reaction mixture was heated under reflux for 2 hr, cooled and treated with ethanediol to decompose excess lead tetraacetate. The product was separated into acidic and neutral portions. The acid portion was the starting **44** (1.9 g). The neutral part on vacuum distillation under reduced pressure furnished **45** (5.1 g), yield 83%; b.p. 110°/0.5 mm; (lit.[26] b.p. 133°/11 mm).

5-*Chloro*-1-*phenylpentan*-1-*one* (**47**)

Chlorodecarboxylation of **46** was carried out as described above to furnish **47** in 86% yield, m.p. 47-49° (lit.[27] 49-50°).

5-Benzoylpentanenitrile (**49**)

Reaction of **47** with NaCN in DMSO at 25° for 12 hr furnished **49** in 80% yield; m.p. 68-69° (lit.[28] m.p. 69-71°).

4-Benzoylbutanenitrile (**50**)

A mixture of **57** (0.287 g), acetone (20 ml), water (10 ml) and *p*-toluenesulphonic acid (0.1 g) was heated under reflux for 3 hr. Usual work-up followed by recrystallization of product from ethanol-pet. ether furnished **50** (0.19 g); yield 83%; m.p. 40-41° (lit.[29] m.p. 40-41°).

Cyclopropyl phenyl ketone (**53**)

Reaction of **45** with NaCN in DMSO at 25° for 48 hr furnished **53** in 82% yield, identified by direct comparison (GLC, PMR) with an authentic sample.

4,4-Ethylenedioxy-4-phenylbutyl iodide (**56**)

Tosylate (**55**) was prepared in 81% yield via tosylation of **54** with pyridine, *p*-toluene sulphonyl chloride at 5° for 20 hr. A mixture of **55** (1.4 g), NaI (7.0 g) and acetone (50 ml) was heated under reflux for 6 hr. Work-up followed by recrystallization of reaction product from pet. ether furnished **56** (1.1 g); yield 89%; m.p. 71-72° (Found: C, 45.6; H, 4.8. $C_{12}H_{15}IO_2$ requires C, 45.3; H, 4.7%).

5,5-Ethylenedioxy-5-phenylpentanenitrile (**57**)

A mixture of **56**, NaCN and DMSO was stirred at 25° for 24 hr to furnish **57** in 85% yield, m.p. 44-46° (Found: C, 72.0; H, 7.1. $C_{13}H_{15}NO_2$ requires C, 71.9; H, 7.0%).

Benzyl cyclopropyl ketone (**58**)

A mixture of **62**, NaCN and DMSO was stirred at 25° for 24 hr to furnish **58** in 78% yield identified by comparison (GLC, PMR) with an anthentic sample.

4,5-Epoxy-5-phenyl-1-chloropentane (**59**)

Bromination of **47** furnished the ketone (**48**) in 96% yield. Reduction of **48** with $NaBH_4$-$NaHCO_3$ furnished **59** in 82% yield; b.p. 107°/0.8 mm; PMR: 4.06 (1H, *d*, $J = 4$ Hz, benzylic H) (Found: C, 67.6; H, 6.7. $C_{11}H_{13}ClO$ requires C, 67.2; H, 6.6%).

1-Cyano-4,5-epoxy-5-phenylpentane (**60**)

A mixture of **59**, NaCN and DMSO was stirred at 25° for 24 hr to furnish **60** in 90% yield; b.p. 128°/0.3 mm (Found: C, 76.7; H, 7.2. $C_{12}H_{13}NO$ requires C, 77.0; H, 7.0%).

1-Bromo-5,6-epoxy-6-phenylhexane (**61**)

Bromination of **51**[30] furnished the haloketone **52** in almost quantitative yield which on reduction with $NaBH_4$-$NaHCO_3$ furnished **61** in 90% yield; b.p. 150° (bath)/0.4 mm, PMR: 4.0 (1H, *d*, $J = 4$ Hz; benzylic H) (Found: C, 55.6; H, 5.8. $C_{12}H_{15}BrO$ requires C, 56.4; H, 5.9%).

5-Chloro-1-phenylpentan-2-one (**62**)

BF_3-etherate catalysed rearrangement of **59** furnished **62** in 90% yield; b.p. 135° (bath)/0.3 mm; IR: 1710 (C=O) (Found: C, 66.8; H, 6.8. $C_{11}H_{13}ClO$ requires C, 67.2; H, 6.6%).

5-Oxo-6-phenylhexanenitrile (**63**)

BF_3-etherate catalysed rearrangement of **60** furnished **63** in 84% yield; b.p. 173/0.9 mm (lit.[31] b.p. 173/0.9 mm); IR: 2240 (C≡N); 1710 (C=O).

6-Bromo-1-phenylhexan-2-one (**64**)

BF_3-etherate catalysed rearrangement of **61** furnished **64** in 75% yield; b.p. 150° (bath)/1 mm; IR: 1710 (C=O) (Found: C, 56.4; H, 5.9. $C_{12}H_{15}BrO$ requires C, 56.4; H, 5.9%).

6-Oxo-7-phenylheptanenitrile (**65**)

Reaction of **64** with NaCN in DMSO at 25° for 24 hr furnished **65** in 92% yield; b.p. 165° (bath)/0.35 mm; (lit.[31] b.p. 149°/0.2 mm); IR: 2240, 1710.

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New Aziridines & Pyrazolines Derived from Diarylidenecycloalkanones†

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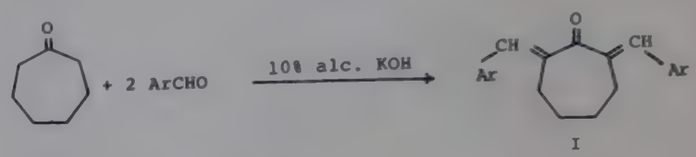
A number of diarylidenecycloalkanones (I and II) have been prepared by the condensation of cycloalkanones with different aromatic aldehydes. Treatment of I and II with bromine gives the corresponding tetrabromides (III and IV). Compounds III react with methylamine to give the aziridine derivatives (V) while with diethylamine they afford the tetradiethylamino products (VI). The diarylidenes (II) on reaction with hydrazine hydrate produce the parent pyrazolines (VIII) of which VIIIb is converted into the pyrazoline derivatives IXb-XIIIb by treatment with different reagents. The reaction of I with diazomethane has also been investigated.

In continuation of our work on mono- and di-arylidene derivatives[1-8] we have prepared the diarylidenecycloheptanones (Ia-e) and the dinaphthylidenecyclohexanones (IIa and IIb) by the base-catalysed condensation of the cycloalkanone with aromatic aldehydes[1-5] and studied some of their chemical reactions.

The structures of Ia-e and IIa, b were confirmed by their elemental analyses and spectral data. Their IR spectra[9] showed bands at 1650-1670 and 1600 characteristic for the stretching vibrations of the conjugated $>C=C-C=O$ groups. The electronic absorption spectrum of IIa displayed a characteristic band at 353.5 nm corresponding to $\pi \rightarrow \pi^*$ in the conjugated system. This band showed a hypsochormic shift in IVa and appeared at 302.5 nm. Further support for the structures of the 2, 6-dinaphthylidenecyclohexanones (IIa and IIb) was provided by their PMR spectral data.

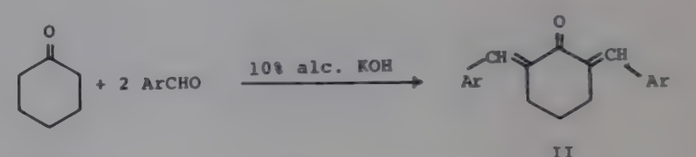
Treatment of Ia-e and IIa, b with two mol of bromine in chloroform gave the corresponding α, α′, 2, 7/6-tetrabromides IIIa-e and IVa, b, respectively. The structures of these tetrabromides were confirmed by their elemental analyses and spectral data. Their IR spectra exhibited a strong and sharp band in the region 1680-1720 due to carbonyl function. This band recorded a shift of about 30 cm^{-1} to higher frequency compared to the corresponding diarylidenecycloalkanones (I, II).

The reactions of tetrabromides IIIa-c with both primary and secondary amines were explored



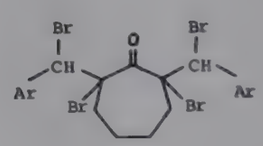
I

Ar = a, C_6H_5- ; b, p-$CH_3C_6H_4$- ; c, p-$CH_3OC_6H_4$- ; d, p-ClC_6H_4-; e, p-BrC_6H_4-

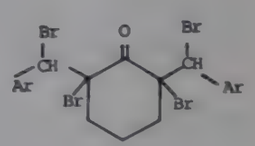


II

Ar = a, α-naphthyl- b, β-naphthyl-



III



IV

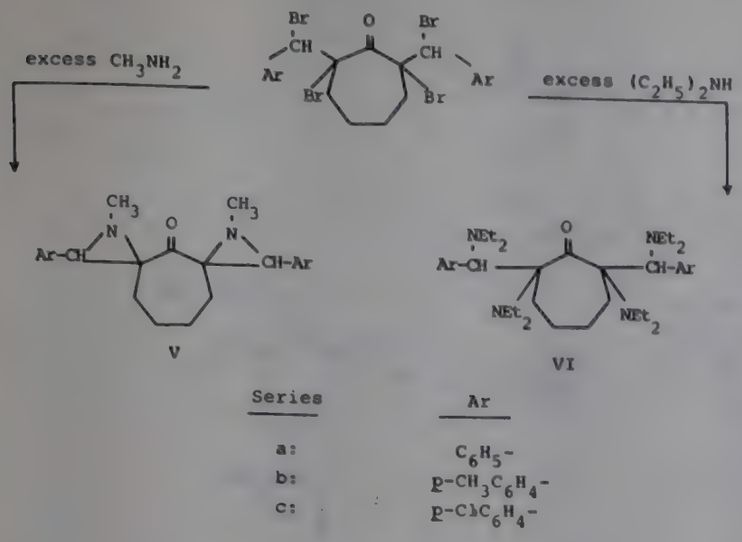
Ar	
IIIa:	C_6H_5-
IIIb:	p-$CH_3C_6H_4$-
IIIc:	p-$CH_3OC_6H_4$-
IIId:	p-ClC_6H_4-
IIIe:	p-BrC_6H_4-

Ar	
IVa:	α-naphthyl-
IVb:	β-naphthyl-

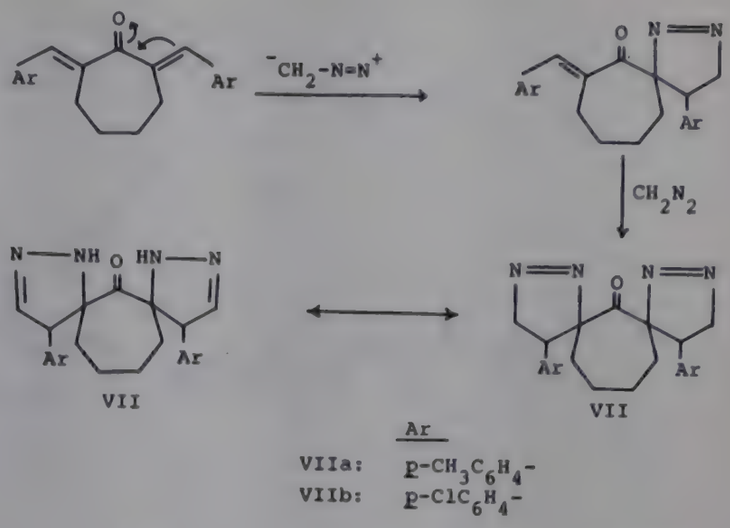
(Scheme 1). With methylamine the corresponding aziridine derivatives (Va-c) were obtained. However, with diethylamine, the corresponding α, α′, 2, 7-tetra-(diethylamino) derivatives (VIa-c) were formed. The structures of V and VI were established by their elemental analyses and IR spectra exhibiting bands at 1630 and 1700 respectively due to $\nu C=O$.

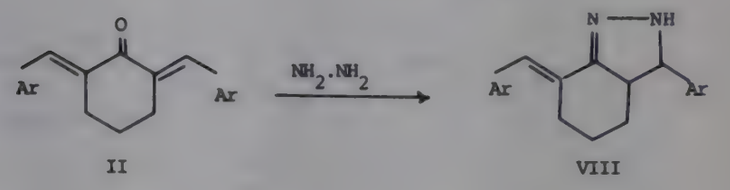
The reactions of I with diazomethane and/or hydrazine hydrate were also investigated. The 2, 7-diarylidenecycloheptanones Ia and Ib reacted with diazomethane to give the dispiropyrazolines VIIa and

†A preliminary report on a part of this work was published in the local Bulletin of the Faculty of Science, El-Mansoura University, Egypt [*Mansoura Bull Sci*, (1981) 8]. Some of the experiments of this work were carried out by the undergraduate trainees R.M. Khalil and M.A. Monshi.

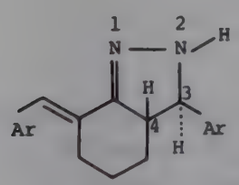


Scheme 1





a, Ar = ∝-naphthyl ; b, Ar = β-naphthyl



(A)

VIIb, respectively. These results are in line with the findings of Moustafa *et al.*[10], who obtained pyrazolines from a similar reaction of diazomethane with arylidenes derived from indanone.

The structures of VII were confirmed by their elemental analyses and IR spectra which showed absorption bands at 1610, 1740 (sh) and 3380 (br) due to >C=N, >C=O and NH functions respectively. The absence of NH band provided additional proof for the suggested structure (VII).

In view of several reports emphasising the pharmacological importance of some bicyclic pyrazoline derivatives[11], we under took the synthesis of a new series of such compounds. The intermediate pyrazolines (VIIIa, b) were obtained by refluxing the respective 2, 6-dinaphthylidenecyclohexanones (IIa, b) with hydrazine hydrate in methanol[8,12,13] (Scheme 2).

On the basis of earlier evidences provided by Krapcho and Turk[11] through shift reagents and PMR decoupling experiments, it is believed that the protons at C-3 and C-4 protons are *trans*-coupled as shown in A.

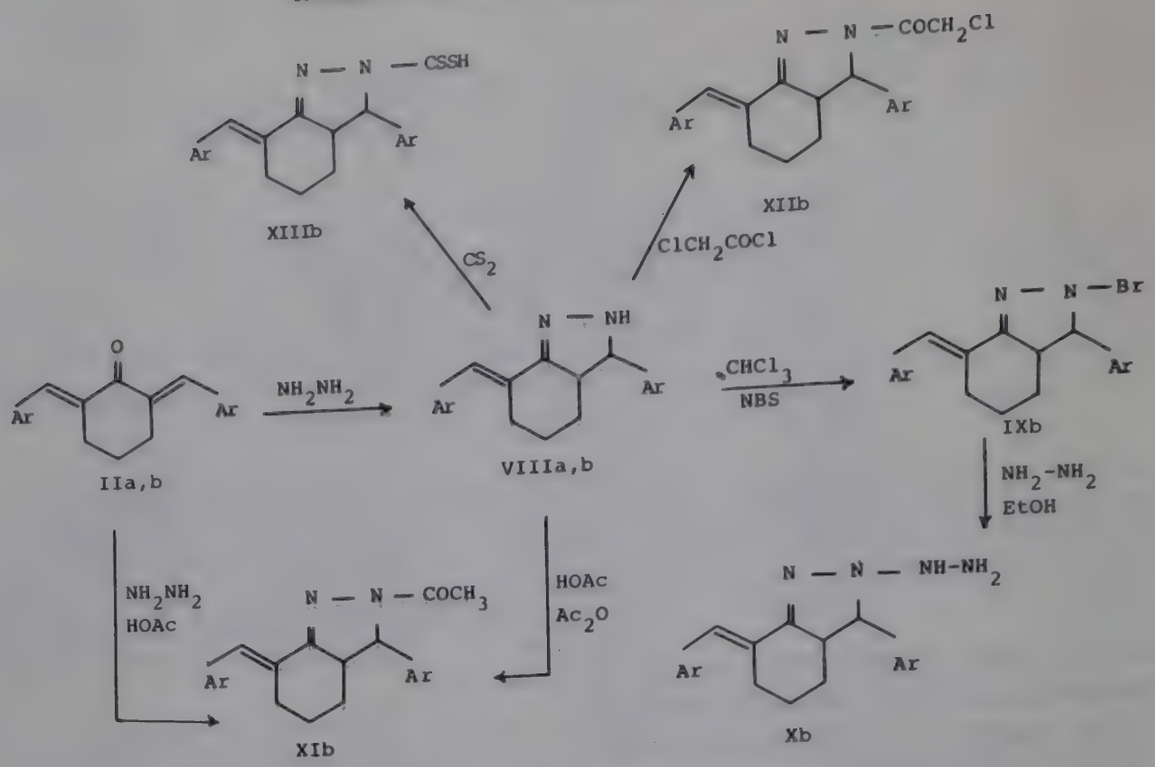
Selective bromination of the pyrazoline VIIIb with N-bromosuccinimide in chloroform as described by Khalaf and coworkers[8,13] gave the N-bromopyrazoline (IXb) which reacted with hydrazine hydrate in ethanol to give the N-hydrazino derivative (Xb). Furthermore acetylation of VIIIb with acetic anhydride in acetic acid gave the N-acetyl derivative (XIb) which was also obtained by the treatment of 2, 6-di-(β-naphthylidene)cyclohexanone (IIb) with hydrazine hydrate in acetic acid. Acetylation of VIIIb with chloroacetyl chloride in dry benzene gave the N-chloroacetyl derivative (XIIb). The hitherto unreported reaction of pyrazoline VIIIb with carbon disulphide produced the N-dithiocarboxypyrazoline derivative (XIIIb). The above reactions are outlined in Scheme 2. The structural assignments of the products VIII-XIII were based on elemental analyses and IR and PMR spectral data.

Experimental Procedure

Melting points are uncorrected. IR spectra were recorded in KBr on a Pye Unicam SP 1100 spectrophotometer (ν_{max} in cm^{-1}). Analyses were carried out in the microanalytical laboratories of King Abdul-Aziz and Cairo Universities. 90 MHz PMR spectra were recorded on a Varian-EM390 instrument. Characterization data of the reported compounds are given in Table 1.

Diarylidenecycloalkanones (Ia-e and IIa, b)

A mixture of aldehyde (2 mol) and cycloalkanone (1 mol) in ethanol (5 ml of ethanol per g of the aldehyde-ketone mixture) was treated with few ml of 15% ethanolic sodium hydroxide. The reaction mixture was stirred in an ice-bath for 4 hr. The precipitated solid after leaving for overnight, was filtered, washed several times with water and once with ethanol, and recrystallised from a proper solvent to give the corresponding diarylidene derivative (Table 1).



a series : Ar = α-naphthyl
b series : Ar = β-napthyl

Scheme 2

Conversion of diarylidenecycloalkanones (I, II) into tetrabromides (IIIa-e and IVa, b)

To a warm stirred solution of I or II (1 mol) in chloroform (10 ml of chloroform/g of the diarylidene compound), a chloroform solution of bromine (2 mol) was gradually added during 1 hr. Thereafter, the reaction mixture was left aside for additional 1 hr, the solvent evaporated slowly in a fuming cupboard, and the solid obtained washed several times with pet. ether (b.p. 40-60°) and recrystallised from a proper solvent to give the corresponding tetrabromide III or IV.

Action of methyl and/or diethylamine ondiarylidene-cycloheptanone tetrabromides (IIIa-c): Formation of aziridines (Va-c) and N-diethylamino derivatives (VIa-c)

A solution of III (1 mol) in the amine (4 mol) was heated under reflux in an oil-bath at 150-170° for 1 hr. The reaction mixture was cooled, and 10 ml of ether added to it. The precipitated solid was filtered, washed several times with ether, dried and recrystallised from a suitable solvent to give V or VI (Table 1).

Action of diazomethane on Ia, b: Formation of dispiropyrazolines (VIIa, b)

To an ice-cold solution of Ia or Ib (1 mol) in ether, a cold solution of diazomethane was added gradually with continuous shaking. After the addition was over, the reaction mixture was left in an ice-box overnight, and the separated solid filtered. An additional amount of the product was obtained by distilling off the solvent. The product was crystallised from a proper solvent to get VIIa or VIIb (Table 1).

3-Naphthyl-7-naphthylidene-3, 3a, 4, 5, 6, 7-hexahydro-2H-indazoles (VIIIa, b): General procedure

A mixture of II (3.74 g, 0.01 mol) and hydrazine hydrate (98%) (2.50 g, 0.05 mol) in methanol (100 ml) was stirred under reflux for 1.5 hr, cooled and kept at 0° for 24 hr. The precipitated product was filtered, washed with methanol, then with pet. ether (b.p. 60-80°) and recrystallised from methanol-hydrazine hydrate (30; 1 v/v) to yield the corresponding indazole VIIIa or VIIIb (Table 1). The pure product was kept in dark bottle in a refrigerator.

2-Bromo-3-(β-naphthyl)-7-(β-naphthylidene)-2, 3a, 4, 5, 6, 7-hexahydro-2H-indazole (IXb)

An equimolar mixture of VIIIb (1.99 g, 0.005mol) and N-bromosuccinimide (0.89 g) in 30 ml of chloroform was stirred under direct sunlight for 2 hr. The precipitated product (IXb) was filtered, washed thoroughly with water and then with benzene, air-dried and recrystallised from a proper solvent (Table 1).

2-Hydrazino-3(β-naphthyl)-7-(β-naphthylidene)-3, 3a, 4, 5, 6, 7-hexahydro-2H-indazole (Xb)

An equimolar mixture of IXb (2.38 g, 0.005 mol) and

Table 1—Characterization Data of the Various Compounds Prepared

Compd	Crystallized from	m.p. °C	Yield (%)	Mol. formula	Found (%) (Calc.)				
					C	H	N	Cl	Br
Ia	EtOH	118	25	$C_{21}H_{20}O$	89.9	6.8	—	—	—
					(87.5	6.9	—	—	—)
Ib	EtOH	170	20	$C_{23}H_{24}O$	87.1	7.6	—	—	—
					(87.3	7.6	—	—	—)
Ic	EtOH	145	24	$C_{23}H_{24}O_3$	79.8	6.8	—	—	—
					(79.3	6.9	—	—	—)
Id	EtOH	158	28	$C_{21}H_{18}Cl_2O$	70.8	5.0	—	19.5	—
					(70.8	5.1	—	19.7	—)
Ie	EtOH	137	30	$C_{21}H_{18}Br_2O$	56.6	3.9	—	—	36.1
					(56.5	4.0	—	—	35.9)
IIa	EtOH	200	62	$C_{28}H_{22}O$	89.5	5.9	—	—	—
					(89.9	5.9	—	—	—)
IIb	EtOH	176	54	$C_{28}H_{22}O$	89.8	6.0	—	—	—
					(89.8	5.9	—	—	—)
IIIa	C_6H_6-pet. ether (80-100°)	117	68	$C_{21}H_{20}Br_4O$	41.4	3.3	—	—	52.1
					(41.5	3.3	—	—	52.6)
IIIb	C_6H_6-pet. ether (80-100°)	212	75	$C_{23}H_{24}Br_4O$	43.9	3.6	—	—	50.7
					(43.4	3.8	—	—	50.3)
IIIc	C_6H_6-pet. ether (80-100°)	185	81	$C_{23}H_{24}Br_4O_3$	41.5	3.7	—	—	48.1
					(41.3	3.6	—	—	47.7)
IIId	C_6H_6-pet. ether (80-100°)	198	76	$C_{21}H_{18}Cl_2Br_4O$	37.2	2.8	—	—	47.6
					(37.3	2.7	—	—	47.3)
IIIe	C_6H_6-pet. ether (80-100°)	208	80	$C_{21}H_{18}Br_6O$	33.2	2.4	—	—	62.2
					(32.9	2.4	—	—	62.7
IVa	C_6H_6-pet. ether (80-100°)	205	43	$C_{28}H_{22}Br_4O$	48.0	3.4	—	—	—
					(48.4	3.2	—	—	—)
IVb	C_6H_6-pet. ether	178	61	$C_{28}H_{22}Br_4O$	48.1	3.4	—	—	—
					(48.4	3.2	—	—	—)
Va	EtOH	146	71	$C_{23}H_{26}N_2O$	79.8	7.4	7.9	—	—)
					(79.8	7.5	8.1	—	—)
Vb	EtOH	170	80	$C_{25}H_{30}N_2O$	80.1	8.2	7.8	—	—
					(80.2	8.0	7.5	—	—)
Vc	EtOH	181	78	$C_{23}H_{24}N_2Cl_2O$	66.3	5.7	6.5	17.2	—
					(66.7	5.8	6.8	16.9	—)
VIa	EtOH	210	76	$C_{29}H_{40}N_4O$	75.5	8.9	12.3	—	—
					(75.7	8.7	12.2	—	—)
VIb	EtOH	185	80	$C_{31}H_{44}N_4O$	76.7	9.2	11.2	—	—
					(76.2	9.0	11.5	—	—)
VIc	EtOH	208	83	$C_{29}H_{38}N_4Cl_2O$	65.6	7.1	10.5	13.1	—
					(65.9	7.2	10.6	13.3)	
VIIa	C_6H_6	142	32	$C_{25}H_{28}N_4O$	74.9	7.1	14.2	—	—
					(75.0	7.0	14.0	—	—)
VIIB	C_6H_6	129	26	$C_{23}H_{22}N_4Cl_2O$	62.3	4.9	12.4	15.8	—
					(62.7	5.0	12.7	15.9	—)
VIIIa	CH_3OH-hydrazine hydrate (30:1 by volume)	92	67	$C_{28}H_{24}N_2$	86.8	5.9	7.4	—	—
					(86.6	6.2	7.2	—	—)
VIIIb	CH_3OH-hydrazine hydrate (30:1 by volume)	141	76	$C_{28}H_{24}N_2$	86.2	6.1	7.3	—	—
					(86.6	6.1	7.2	—	—)
IXb	C_6H_6	271	40	$C_{28}H_{23}BrN_2$	72.1	4.8	16.5	—	—
					(72.0	4.9	16.7	—	—)
Xb	C_6H_6	202	57	$C_{28}H_{26}N_4$	80.8	6.0	13.6	—	—
					(80.4	6.2	13.4	—	—)
XIb	C_6H_6	187	84	$C_{30}H_{26}N_2O$	84.1	5.9	6.3	—	—
					(83.7	6.0	6.5	—	—)
XIIb	C_6H_6	226	63	$C_{30}H_{25}ClN_2O$	77.7	5.4	6.5	—	—
					(77.5	5.4	6.0	—	)
XIIIb	C_6H_6	129	75	$C_{30}H_{24}N_2S_2$	75.9	5.5	5.9	—	—
					(75.7	5.2	6.0	—	—)

hydrazine hydrate (0.25 g) in 30 ml of ethanol was heated under reflux for 30 min, cooled and the resulting solid collected, washed with dil. ammonia, air-dried and recrystallised from a suitable solvent (Table 1).

2-Acetyl-3-(β-naphthyl)-7-(β-naphthylidene)-3, 3a, 4, 5, 6, 7-hexahydro-2H-indazole (XIb)

(a) A mixture of IIb (3.74 g, 0.01 mol) and hydrazine hydrate (98%) (2.50 g, 0.05 mol) in gl. acetic acid (100 ml) was stirred under reflux for 1 hr, cooled and kept at 0° overnight. The precipitated product was filtered, washed with pet. ether (b.p. 40-60°) and recrystallised from a proper solvent to give XIb (Table 1).

(b) A solution of VIIIb (1 g) in a mixture of gl. acetic acid and acetic anhydride (25 ml; 10:1 ratio) was refluxed for 1 hr, cooled in a refrigerator and left overnight. The solid separated was filtered, washed several times with pet. ether (b.p. 40-60°) and crystallised from benzene to yield XIb (0.8 g; 73%).

2-Chloroacetyl-3-(β-naphthyl)-7-(β-naphthylidene)-3, 3a, 4, 5, 6, 7-hexahydro-2H-indazole (XIIb)

To a solution of VIIIb (3.88 g, 0.01 mol) in benzene (50 ml), was added chloroacetyl chloride (1.34 g, 0.012 mol) dropwise under stirring, and the reaction mixture stirred for an additional 1 hr. The benzene layer was evaporated *in vacuo* and the solid triturated with water, filtered and recrystallised from a proper solvent to give XIIb (Table 1).

3-(β-Naphthyl)-7-(β-naphthylidene)-3, 3a, 4, 5, 6, 7-hexahydro-2H-indazole-2-carbodithioic acid (XIIIb)

The pyrazoline derivative VIIIb (1.99 g, 0.005 mol) was added to an excess amount (20 ml) of cold dry carbon disulphide. The resultant clear solution was kept at 0° for 48 hr, and the precipitated solid crystallised from a suitable solvent to get XIIIb (Table 1).

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Chemistry of Carbenes: Part IV—Reactions of Methylene with Diisopropyl Ether

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The insertion of methylene into a tertiary C – H bond is 1.5 times and into Pr^i – O 0.78 times as fast as insertion into a primary C – H bond. The abstraction of secondary hydrogen in diethyl ether being ~0.11 at 16°C, the H-abstraction of tertiary hydrogen in diisopropyl ether is ~8 times at 16°C and 15 times at 190°C. Possibly the monoradicals formed augment the H-abstraction rates of the biradicals. The activation energy differences for insertion reactions are very low suggesting that the absolute values are very low too. In this respect the insertion reactions differ from abstraction reactions which have higher temperature coefficient activation energies and *A*-factors. Studies on the role of CO_2 and O_2 on the course of these reactions show that CO_2 is not truly inert, whereas oxygen reacts with isopropyl radicals to give rise to acetone thereby lowering the yield of dimer, biisopropyl. The bond reactivities of all the ethers studied so far are also summarized. The authenticity of the proposed mechanism of the various reactions is based on the product ethers, and lower hydrocarbons arising as by-products.

In earlier communications[1-3], reactions of methylene with primary and secondary C – H bonds in both symmetrical and asymmetrical ethers have been reported. This paper deals with the reactions of methylene with tertiary bonds of a symmetrical ether, namely diisopropyl ether.

Materials and Methods

The experimental procedure and analytical technique for the separation and identification of products has been described earlier[1].

Results and Discussion

Insertion reaction

The insertion reaction, as before, yielded two higher ethers by the attack at $\overset{3}{\underset{}{}}$ C – H or at $\overset{1}{\underset{}{}}$ C – H bond. Pr^iOBu^s was predominant as would be expected since there are twelve $\overset{1}{\underset{}{}}$ C – H bonds available in comparison to two $\overset{3}{\underset{}{}}$ bonds. The molar ratios Pr^iOBu^t/Pr^iOBu^s at various temperatures were measured and the averages of several values are presented in Table 1. At 16°C, the molar ratio of Pr^iOBu^t/Pr^iOBu^s was 0.25. Insertion into any given tertiary C – H bond is thus 1.5 times as rapid as insertion into primary C – H bond. Table 1 also shows the average molar ratio at higher temperatures when the value 0.25 at 16°C falls to 0.15 at 190°C.

Measurements were also made on the absolute amount of Pr^iOBu^s formed in the presence of air. It was found that with the addition of air up to 2.1 cm pressure an increase in the yield of this ether occurred. Thereafter the yield decreased slightly up to 13 cm and beyond 13 cm it attained a constant value. In contrast the yield of Pr^iOBu^t decreased continuously with increase of added air, and at 16.6 cm only a trace appeared, suggesting that the Pr^iOBu^t was formed in an activated state which was capable of reacting with oxygen.

Table 1—Average Values (Molar Ratios) for Products Normalized to Pr^iOBu^s in Reaction of Methylene with Diisopropyl Ether

Temp (°C)	Biisopropyl	$MeOPr^i$	Pr^iOBu^t	Acetone
16	nil	0.13	0.25	0.22
68.7	0.07	0.09	0.18	0.72
100	—	0.09	0.17	1.19
132	0.17	0.08	0.16	1.86
190	0.43	0.09	0.15	3.30
	Effect of carbon dioxide			
15-17	—	0.08	0.32	0.40
132 (with added (CO_2, 0.5-36 cm Hg)	0.28	0.06	0.16	Varies with CO_2
	Accuracy of results			
16			±0.02	±0.03
68			±0.003	±0.03
100			±0.003	±0.03
132			±0.003	±0.025

An estimate of the difference of activation energies and the relative *A*-factors for the two insertion reactions forming Pr^iOBu^t and Pr^iOBu^s by steps (a) and (b) can be made by plotting the product ratio Pr^iOBu^s/Pr^iOBu^s against 1/T. This gave $E_2 - E_1 = 0.9$ kcal mol^{-1} and $A_1/A_2 = 0.053$. The relative *A*-factor for individual C – H bond is $A_1/A_2 = 0.31$. The effect of *E* and *A*-factors thus tend to cancel out.

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$$:CH_2 + Pr^iOPr^i \rightarrow Pr^iOBu^t \quad ...(a)$$

$$:CH_2 + Pr^iOPr^i \rightarrow Pr^iOBu^s \quad ...(b)$$

Displacement reaction

The attack of methylene on Pr^iOPr^i also gave methyl isopropyl ether by the displacement reaction (c) observed in the previous work[1-3].

$$:CH_2 + Pr^iOPr^i \rightarrow MeOPr^i + C_3H_6 \quad ...(c)$$

At room temperature the relative rate of formation of this ether was 0.13. At 68.7 and 190°C the relative rate was 0.09 (Table 1). The other product of the reaction, propylene, was determined on an adsorption column.

Abstraction reaction

Methylene has been found to abstract tertiary hydrogen from the isopropyl group of Pr^iOPr^i. This reaction is about 13 times faster than the abstraction of secondary hydrogen from diethyl ether.

The abstraction reaction gave rise to acetone and lower hydrocarbons which were formed as a result of free radical reactions. The lower hydrocarbons found were methane, ethane, propane, propylene, 2,3-dimethylbutane (biisopropyl) and isobutane. Of these, methane was not measured quantitatively as it was by far the smallest in amount. The relative yields of ethane, propane, propylene and isobutane have been determined and their yields, normalized to acetone, are given in Table 2. The relative yields of 2,3-dimethylbutane normalized to Pr^iOBu^s are given in Table 1. The mechanism (steps 1-6; Scheme 1) is proposed for the products resulting from the abstraction reaction:

$$:CH_2 + (CH_3)_2CHOCH(CH_3)_2 \rightarrow .CH_3 + \text{iso-}C_3H_7OC(CH_3)_2 \quad ...(1)$$

$$\text{iso-}C_3H_7OC(CH_3)_2 \rightarrow (CH_3)_2CO + \text{iso-}C_3H_7 \quad ...(2)$$

$$2(\text{iso-}\dot{C}_3H_7) \rightarrow (CH_3)_2CHCH(CH_3)_2 \quad ...(3)$$

$$2(\text{iso-}\dot{C}_3H_7) \rightarrow C_3H_6 + C_3H_8 \quad ...(4)$$

$$.CH_3 + \text{iso-}\dot{C}_3H_7 \rightarrow (C_3H_6 + CH_4) \text{ or iso-}C_4H_{10} \quad ...(5)$$

$$.CH_3 + .CH_3 \rightarrow C_2H_6 \quad ...(6)$$

Scheme 1

Owing to the high activation energies (7-10 kcal) of abstraction by large monoradicals, no further abstraction is likely at 20°C. The iso-$C_3\dot{H}_7OC(CH_3)_2$ radical apparently decomposes readily into acetone and an isopropyl radical. Such a decomposition has also been postulated[4,5] for the H-abstraction by methyl radicals. Recombination of isopropyl and methyl by steps (3), (5) and (6) results in the formation of 2,3-dimethylbutane, isobutane and ethane found in the products. The propylene and propane obtained in the products arise from mixed disproportionation[6] (step-4), a process which competes with step-3 and is faster than the latter. The recombination of the free radicals has almost no activation energy and therefore considerable amounts of these products are formed. The yield of 2,3-dimethylbutane formed in step-3 increases manifold in the temperature range 68.7° to 190°C. The relative yields of ethane, propane, propylene, and isobutane at 100°C, given in Table 2, show that the yields are likely to be higher at higher temperatures. The fact that butane is not equimolar in amount to propane is because of the contribution of step-5 and because of the displacement reaction.

Table 2—Molar Ratios of Formation of Byproducts at 100 C

Irradiation: Ketene + Pr^iOPr^i at 100 C
Column: F(DNP)S* + Act. Alumina Column (12 ft) (20-40 Mesh)
N_2 flow rate: 17 c c s/min
Column temp: 43 C

Ether	Ketene	Molar ratios normalized to acetone			
P cm	P cm	Ethane	Propane	Propylene	Iso-butane
10.2	1.4	—	0.06	0.13	0.24
7.5	1.5	0.03	0.08	0.2	0.23
9.9	1.2	0.02	0.05	(0.09)	(0.14)
8.0	2.8	0.01	0.05	0.11	0.20
6.8	2.0	0.02	0.06	0.15	0.22
	Av:	0.02	0.06	0.15	0.22
Molar ratio (at 100):		0.19	0.19	0.47	0.27

*Packing: firebrick powder treated with dinonyl phthalate (20-40 mesh).

If the above mechanism is correct, then acetone and lower hydrocarbons must be produced in equivalent amounts, viz. the yields of acetone and hydrocarbons should be related by Eq. (7)

$$\frac{[\text{Propane}]}{[\text{Acetone}]} + \frac{[\text{Propylene}]}{[\text{Acetone}]} + \frac{[\text{Isobutane}]}{[\text{Acetone}]} = 1.00 \quad ...(7)$$

where [propylene] is given by subtracting the propylene formed in displacement reaction from experimental yield. From Fig. 1 the value for biisopropyl at 100°C comes to 1.06 and hence biisopropyl/acetone = 0.11. Propylene from abstraction reaction comes to 0.39 (0.47-0.08) and the equivalent yield of iso-C_3H_7 adds up to 1.07 as given in Table 3.

The results of Table 3 prove, within experimental limits of error, the authenticity of the proposed mechanism. Only the abstraction of tertiary hydrogen leads to acetone formation, and the production of an approximately equimolar amount of hydrocarbons shows that abstraction of primary atoms is likely to be unimportant.

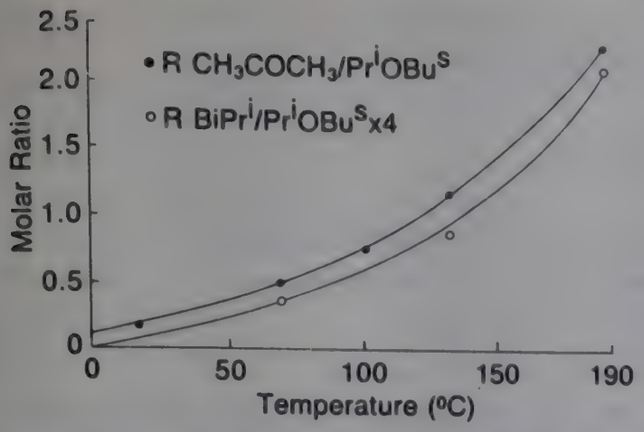

Fig. 1—Variation of relative molar yield of acetone and biisopropyl with temperature

Table 3—Calculation of Equivalent Yield of Isobutane

Hydrocarbon	Molar yield relative to acetone	Equiv. yield of iso-C_3H_7
2,3-Dimethylbutane	0.11	0.22
Propane	0.19	0.19
Propylene		
(a) Total	0.47	
(b) Displacement	0.08	
(c) Abstraction	0.39	0.39
Isobutane	0.27	0.27
	Total:	1.07

Temperature dependence of the abstraction reaction

The yields of the products of abstraction reaction from ethers were found to increase greatly with increase in temperature. Thus, the molar rate of abstraction/bond for tertiary hydrogen based on unity for insertion into 1° C—H in Pr^iOPr^i, for example, is 1.3 at 16°, 4.3 at 68.7°, 7.1 at 100°, 11.1 at 132°, and 19.8 at 190°C. In view of the large variation in the relative molar yields of acetone with temperature the activation energy differences between the abstraction and insertion reactions (steps 8 and 9) respectively were calculated

$$:CH_2 + (\text{iso-}C_3H_7)_2O \xrightarrow{k_1} (CH_3)_2CO + \text{lower hydrocarbons} \quad ...(8)$$

$$:CH_2 + (\text{iso-}C_3H_7)_2O \xrightarrow{k_2} Pr^iOBu^s \quad ...(9)$$

$$R_{acetone} = k_1[:CH_2][Pr^iOPr^i] \quad ...(10)$$

$$R_{Pr^iOBu^s} = k_2[:CH_2][Pr^iOPr^i] \quad ...(11)$$

Therefore, $R_{acetone}/R_{Pr^iOBu^s} = k_1/k_2$ which is known from the relative rate of acetone formation at different temperatures. An Arrhenius plot of these values gave $E_1 - E_2 = 3.8$ kcal/mol and the $A_1/A_2 = 1.32 \times 10^2$.

Since the rate of H-abstraction increased at higher temperatures, the production of methyl and isopropyl radicals also must increase. Table 1 shows that the recombination: iso-C_3H_7 + iso-C_3H_7 → biisopropyl increases as the reaction temperature is increased. The increase is gradual from 68.7° to 132°C but more marked at higher temperature (Fig. 1). As these reactions are closely connected to those giving other hydrocarbons, it is very likely that their relative rates are affected in a similar manner.

Effect of carbon dioxide

The role of not truly inert carbon dioxide in the reaction of methylene with Pr^iOPr^i was followed in some detail at 16° and 132°C. At 16°, the relative rate of insertion product, Pr^iOBu^t, showed small increase from 0.25 to 0.32 but at 132°C there was no change from the value.

The displacement reaction showed a decrease for relative amounts of $MeOPr^i$ from 0.13 to 0.09 on the addition of 36.4 cm CO_2 at room temperature. Similarly at 132°C, the value showed a small decrease from 0.08 to 0.06. The relative yield of acetone also showed an increase from 0.22 to 0.40 at 16°C but at 132°C the relative yield decreased in the presence of CO_2. The variation being large, an average could not be taken. At 132°C, the relative yield of biisopropyl increased from 0.17 to 0.21 in the presence of CO_2, indicating that CO_2 was reactive at higher temperatures in these systems.

Effect of oxygen

The reaction of methylene with Pr^iOPr^i at 132°C in the presence of O_2 was investigated. Random pressures of air added were chosen and up to about 23 cm air was introduced to the system. Acetone formation increased manifold with increase in air pressure in the system. When the relative yields obtained were plotted against the air pressure, marked rise in the curve was obtained, similar to the one obtained for acetaldehyde from the reaction of methylene with diethyl ether[1].

The relative yield of biisopropyl is much lower (0.07) than that (0.17) obtained in the absence of air, although at low air pressures the relative yields of both acetone and biisopropyl show an increase. The decrease in biisopropyl is presumably due to the oxidation of isopropyl radicals before they could dimerize. Reactions (12-14) may occur

$$\text{iso}\dot{C}_3H_7 + O_2 \rightarrow \text{iso}C_3H_7OO \quad ...(12)$$

$$\text{iso-}C_3H_7OO\cdot \rightarrow \begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!C=O \rightleftharpoons OH \quad ...(13)$$

$$(\text{iso-}C_3H_7)_2O + \cdot OH \rightarrow \text{iso-}C_3H_7O\dot{C}_3H_6 + H_2O \quad ...(14)$$

Isopropyl radical may give rise to acetone according to steps (12) and (13). The activation energy for the reaction (15)

$$\cdot CH_3 + O_2 \rightarrow \cdot CHO + H_2O \quad ...(15)$$

has been estimated to be 1.5 kcal by Van Tiggelen[7] from the oxidation of methane photosensitized by acetone. Steacie[8] estimated it to be ~0.

It seems unlikely that E_{12} will be much higher than 1 kcal or so as it is similar to E_{15}. A high proportion of iso-C_3H_7 radicals should be oxidized in the presence of oxygen. The increased yield of acetone (more than five times) suggests that short chains can occur in the presence of oxygen and that much more reactive radicals than CH_3 must be formed. Hydroxyl radical ·OH is the most obvious choice although there is no direct evidence for reaction (13). Isobutane is largely a product of recombination of isopropyl and methyl radicals generated in the system and its yield decreases considerably with the addition of air. Propylene, as expected, shows a similar trend in view of the fact that the radicals are getting readily oxidized.

The products of insertion reaction, $MeOPr^i$ and Pr^iOBu^t at 132°C remain unaffected by the addition of air up to 22.9 cm (Table 1). On an average a value of 0.09 compared to 0.08 in the absence of air was obtained.

Lower hydrocarbons

The H-abstraction reaction by methylene gives rise to methyl radicals[9] which can dimerize to yield ethane (step-19). Frey and Kistiakowsky[10] have postulated this reaction in the attack of $:CH_2$ on alkanes where the relative yield of ethane was the same whether propane or butane was used. All methyl radicals do not dimerize but also disappear by cross combination with other monoradicals. At 100°C, the rate ratio for ethane is 0.02 only (Table 2). The other reactions are:

$$(iso\text{-}C_3H_7)_2O + :CH_2 \rightarrow (CH_3)_2CO + \cdot CH_3 + \cdot CH(CH_3)_2 \quad ...(16)$$

$$\cdot CH_3 + \cdot CH(CH_3)_2 \rightarrow CH_3CH(CH_3)_2 \quad ...(17)$$

$$2\cdot CH(CH_3)_2 \rightarrow \text{2,3-dimethyl butane} \quad ...(18)$$

$$\cdot CH_3 + \cdot CH_3 \rightarrow C_2H_6 \quad ...(19)$$

$$2\cdot CH(CH_3)_2 \rightarrow C_3H_6 + C_3H_8 \quad ...(20)$$

All the products predicted by steps (16) to (20) have been identified and measured quantitatively. This leads to the conclusion that the mechanism of acetone formation is correct. All the reactions of isopropyl and methyl radicals (steps 17-20) have been found to give lower hydrocarbons in equimolar proportions to acetone. Thus, a total of 1.07 lower hydrocarbons was obtained after deducting the amount of propylene formed from displacement reaction, thereby proving the authenticity of the above mechanism.

Bond reactivity of the ethers

The bond reactivity data on the reactions of methylene with all the ethers studied so far[1-3] including the diisopropyl ether in the present investigation are summarized in Table 3. The bond reactivity, as stated earlier, has been calculated after allowing for the difference in the number of bonds concerned. The values for abstraction of secondary and tertiary hydrogens show that the latter value is larger than the former, i.e. 0.31 versus 1.32 at 20° and 1.38 versus 7.14 at 100°C. To obtain the total reactivity of C

Table 4—Bond Reactivity and Products Formed in Insertion and Displacement Reactions of Methylene with Ethers

Ether	Bond attacked (No. of identical bonds)	Product formed (X)	Standard product (S)	100°C		20°C	
				Amount X/S	Bond reactivity	Amount X/S	Bond reactivity
MeOMe	Primary in MeOMe (6)	EtOMe	$EtOPr^n$ (6)	1.72	1.72		
EtOEt	Primary (6)	$EtOPr^n$	$EtOPr^n$ (6)	1.00	1.00	1.00	
	Sec (4)	$EtOPr^i$	$EtOPr^n$ (6)	1.86	2.79	1.75	2.63
	Et−O (2)	MeOEt	$EtOPr^n$ (6)	0.38	1.14	0.46	1.38
$EtOPr^n$	Primary in Pr^n (3)	$EtOBu^n$	Pr^nOPr^n (3)	0.92	0.92	0.87	0.87
	Sec in Pr^n (2)	$EtOBu^s$	Pr^nOPr^n (3)	0.86	1.29	2.3	3.50
	Sec in Pr^n (2)	$EtOBu^i$	Pr^nOPr^n (3)	1.16	1.74		
	Pr-O (1)	MeOEt	Pr^nOPr^n (3)	0.24	0.72	0.20	0.60
	Primary in Et (3)	Pr^nOPr^n	Pr^nOPr^n (3)	1.00	1.00	1.00	1.00
	Sec in Et (2)	Pr^iOPr^n	Pr^nOPr^n (3)	1.22	1.83	1.32	1.98
	Et-O (1)	$MeOPr^n$	Pr^nOPr^n (3)	0.37	1.11	0.30	0.90
Pr^iOPr^i	Primary C−H (12)	Pr^iOBu^n	Pr^iOBu^n (12)	1.00	1.00	1.00	1.00
	Tert C−H (2)	Pr^iOBu^t	Pr^iOBu^n (12)	0.17	1.02	0.25	1.50
	Pri-O (2)	$MeOPr^i$	Pr^iOBu^n (12)	0.09	0.54	0.13	0.78
		Abstraction by methylene					
EtOEt	Sec C−H (4)	CH_3CHO	$EtOPr^n$	0.92	1.38	0.21	0.31
Pr^iOPr^i	Tert C−H (2)	CH_3COCH_3	Pr^iOBu^s	1.19	7.14	0.22	1.32

$-H$ bonds, therefore, the values for abstraction may be added to the insertion values. These are for $\overset{\circ}{2}$ C$-$H, 2.79 and for $\overset{\circ}{3}$ C$-$H, 1.02 at 100°C. This shows the order of total bond reactivities as tertiary > secondary > primary and follows the sequence of bond dissociation energies given by Cottrell[11] as follows:

Bond attacked	Tertiary	Secondary	Primary
Total bond reactivity	8.16	4.17	1.0
Bond strength, kcal mol^{-1}	89	94	96

Table 4 also shows the small and random effects of temperature on the relative insertion rates. The results are within experimental error and show that the activation energy difference between different insertion reactions is at most a few hundred calories. The results agree with those of other workers[12] who have shown that the activation energy for insertion of $:CH_2$ into primary bonds of alkanes is only very slightly different from that for insertion into $\overset{\circ}{2}$ and $\overset{\circ}{3}$ bonds. However, the relative *A*-factors cancel out this difference so that relative rate of attack is approximately, but not exactly, statistical. These results obtained in gas phase contrasted with those of Doering *et al.*[13] who found that in the liquid phase the insertion reaction with both ethers and hydrocarbons was indiscriminate. The present results again confirm the difference between the two phases.

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2-Aryl-3-arylthiocyclohexanones: Synthesis & Stereochemistry

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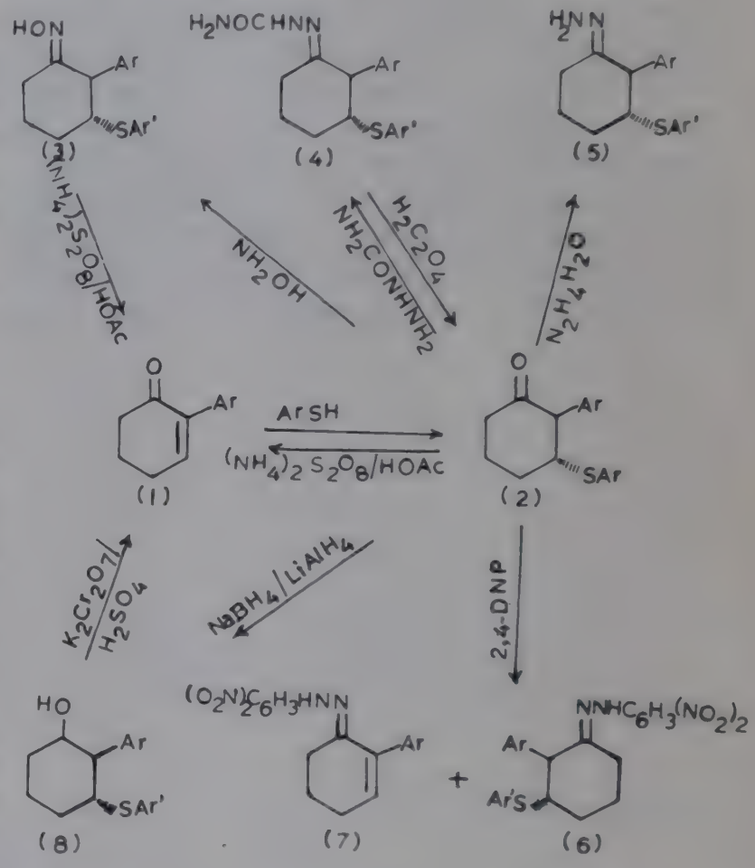
The 1,4-addition of arylthiols to 2-aryl-2-cyclohexen-1-ones (**1**) is described and the stereochemistry of the resultant products (**2**) has been derived as *trans*-diequatorial on the basis of PMR data and chemical reactions.

1,4-Addition reaction across 2-substituted 2-cyclohexen-1-ones is a suitable method for preparing 2,3-disubstituted cyclohexanones. The synthesis of a number of such compounds via. 1,4-addition has already been reported[1,2] from our laboratory. In continuation of this work and in view of the expected biological importance[3] and potential synthetic utility[4], the work on the synthesis of hitherto unknown 2-aryl-3-arylthiocyclohexanones via 1,4-addition reaction was therefore undertaken.

The 1,4-addition of various arylthiols to 2-aryl-2-cyclohexen-1-ones (**1**) was carried out at 25° under nitrogen atmosphere using chloroform as solvent and a trace of triethylamine as catalyst. The yields of the resultant 2-aryl-3-arylthiocyclohexanones (**2**) (Scheme 1) which were shown to be single entities in each case, were generally good ranging from 80 to 95%. The physical and PMR data of these ketones are presented in Table 1.

It is seen from Table 1 that the C_2- and C_3-hydrogens of **2a**, though one being benzylic and the other being α-to the sulphur atom, appeared in the PMR spectra at the same position at δ 3.60. The band-width and $W_{1/2}$ were 15 Hz and 8 Hz respectively. This factor together with the fact that the axial approach of the dienophile (the antiparallel attack) is more favourable leading to an axial product[4-6], led us to conclude (of course deceptively as we see later on) that the compound formed was 2*e*-phenyl-3*a*-phenylthio-cyclohexanone, i.e. a *cis*-isomer. Attempts to separate the C_2- and C_3-hydrogens either by recording the spectrum on a 360 MHz instrument or with complexing agents such as $Eu(DPM)_3$ or in TFA, failed. However, when the PMR spectrum of **2a** was recorded in pyridine-d_5 at 360 MHz, the peaks due to C_2- and C_3-hydrogens got separated and the coupling patterns were distinct showing that both the hydrogens were axial, i.e. *trans* to each other. The C_2-hydrogen appeared as a doublet ($J = 11$ Hz) at δ 3.92 and the C_3-hydrogen as a triplet of doublet at 3.98 ($J = 11$ Hz, 4 Hz). Obviously the downfield shift of both the C_2- and C_3-hydrogens contrary to the pyridine solvent rule



	Ar	Ar'
(a)	Phenyl	Phenyl
(b)	Phenyl	4-Methylphenyl
(c)	Phenyl	4-Methoxyphenyl
(d)	4-Methylphenyl	Phenyl
(e)	4-Methoxyphenyl	Phenyl
(f)	4-Isopropylphenyl	Phenyl
(g)	3,4-Dimethylphenyl	Phenyl
(h)	3-Methylphenyl	Phenyl
(i)	4-Methoxyphenyl	4-Methoxyphenyl
(j)	4-Isopropylphenyl	4-Methylphenyl

Scheme 1

may have to be ascribed to the presence of the polar phenylthio group in this system[7]. Hence, it is confirmed that the product isolated was the thermodynamically more stable 2*e*-aryl-3*e*-arylthio-cyclohexanone. This assignment was also supported by the reactions discussed below:

Table 1—Characterisation and PMR Data of 2*e*-Aryl-3*e*-arylthiocyclohexanones (2)

Compd	Yield (%)	m.p. °C	PMR ($CDCl_3$), δ ppm			
			C_2- and C_3-H	Other aliphatic hydrogens	Ar-*H*	Others
2a	95	144	3.60	1.50-2.60	7.25	
2b	81	128-29	3.60	1.50-2.50	7.00-7.40	2.30 (*s*, $-CH_3$)
2c	93	130-31	3.50	1.50-2.50	6.70-7.40	3.75 (*s*, $-OCH_3$)
2d	85	118-20	3.60	1.60-3.60	7.00-7.40	2.30 (*s*, $-CH_3$)
2e	77	118-20	3.55	1.60-2.60	7.00-7.25	3.75 (*s*, $-OCH_3$)
2f	83	155	3.50	1.50-3.00	7.10-7.50	1.25 [*d*, $-CH(CH_3)_2$]
2g	90	116-18	3.55	1.60-2.60	6.90-7.40	2.20 (*s*, $-CH_3$)
2h	85	111	3.60	1.60-2.60	6.95-7.40	2.35 (*s*, $-CH_3$)
2i	93	108-10	3.50	1.60-2.60	6.70-7.40	3.85 (*s*, $-OCH_3$)
2j	89	67-69	3.60	1.50-2.50	7.10-7.50	2.90 [*m*, $-CH(CH_3)$] 1.30 [*d*, $-CH(CH_3)_2$]

In order to simplify the PMR spectrum of **2a**, so as to separate the C_2- and C_3-hydrogens still more convincingly, it was decided to prepare the corresponding sulphoxide or sulphone under mild conditions, so that the conformation is retained and in which case, the chemical shift value of C_3-hydrogen should be different from that of C_2-hydrogen. As the treatment with either $KMnO_4$ or H_2O_2 at room temperature failed to effect the desired change, the oxidation by ammonium perdisulphate in gl. acetic acid at 100° was attempted. But, in this case also the corresponding sulphoxide or sulphone could not be isolated and the parent enone, viz. 2-phenyl-2-cyclohexen-1-one (**1a**) was obtained in considerable yield. This shows that the sulphoxide formed might have undergone facile pyrolytic elimination to yield the parent enone. This type of *cis*-thermal elimination has already been reported[8] for *cis*-group and this shows that the leaving groups 2-H and 3-PhS are in *cis*-position or in other words 2-Ph and 3-PhS groups are in *trans*-orientation.

On oximation or during the formation of semicarbazone or hydrazone of **2a**, the stereochemistry of the derivatives (**3a**, **4a** and **5a** respectively) was established as **2e**, **3e**. This is well-evidenced by the appearance of a clean doublet of 10 Hz ($J_{2,3}$) and a doublet of triplet ($J_{2,3}=J_{3,4e}=10$ Hz and $J_{3,4e}=3$ Hz) centred at δ 3.55 and 3.65 respectively for the C_2- and C_3-hydrogens. The orientation of the N-substituent in these derivatives could be shown as *anti* to the C_2-substituent based on the chemical shift values of the C_6-equatorial hydrogen as we have observed earlier in other 2,3-disubstituted cyclohexanone derivatives[9]. The fact that the hydrolysis of the semicarbazone **4a** by oxalic acid gave the ketone **2a**, also established that the latter should be a *trans*-diequatorial isomer.

As against the formation of oxime, semicarbazone and hydrazone, the formation of 2,4-dinitrophenylhydrazone of 2*e*-phenyl-3*e*-phenylthiocyclohexanone (**2a**) resulted in two products. The first product obtained on crystallisation was the 2,4-dinitrophenylhydrazone (**6a**) of **2a** as yellow crystals and was identified by its PMR spectrum. The mother liquor after concentration yielded another compound. The red crystals of this second compound was shown to be the 2,4-dinitrophenylhydrazone (**7a**) of **1a** by m.m.p. determination and PMR spectrum. The formation of **7a** can be explained by the acid-catalysed elimination of the 3-phenylthio group followed by the reaction of 2,4-dinitrophenylhydrazine with the resultant enone (**1a**).

It is interesting to note that the oxidation of 2*e*-phenyl-3*e*-phenylthiocyclohexanone oxime (**3a**) by the same method as applied for **2a** using ammonium perdisulphate also gave the enone **1a** and not the corresponding oxime. Here, under the conditions of the reaction, hydrolysis prior to oxidation might have occurred to give the ketone **2a** which yielded the enone **1a**.

Both the sodium borohydride and lithium aluminium hydride reductions of **2a** yielded only one alcohol (**8a**) in each case. The products obtained were shown to be single entities by sharp m.p., TLC and PMR spectra. From the PMR spectrum of **8a**, the compound was assigned the structure as 1*e*-hydroxy-2*e*-phenyl-3*e*-phenylthiocyclohexane, as the C_1- C_2- and C_3-hydrogens which appeared at δ 3.29, 2.45 and 3.70 respectively are all axial hydrogens ($J_{1,2}=9$ Hz; $J_{2,3}=11$ Hz). Thus, the alcohol formed (**8a**) is an all equatorial isomer, as the approach of the hydride through the axial side is not at all hindered[10], once again emphasising the conclusion that the ketone **2a** is a diequatorial isomer.

The attempted oxidation of the alcohol **8a** with ammonium perdisulphate in acetic acid to get the elimination product as in the case of **2a**, was unsuccessful. However, chromic acid oxidation of **8a** led to the parent enone **1a** as in the case of other oxidations discussed above. For obvious reasons, not only the hydroxyl group is oxidised, but the phenylthio group is also eliminated.

The above stereochemistry of the products, established both by the PMR data and chemical reactions, could be explained as the originally formed kinetically-controlled *cis*-product is equilibrated under the reaction conditions to give rise to the thermodynamically more stable *trans*-isomer.

Experimental Procedure

Melting points are uncorrected. PMR spectra were recorded on a Perkin-Elmer R32 90 MHz spectrometer with TMS as internal standard (chemical shifts in δ ppm). The PMR spectra of **2a** were also recorded in $CDCl_3$, DMSO-d_6 and C_5D_5N at 360 MHz. Elemental analyses of the new compounds were within $\pm 0.4\%$ of the theoretical values.

2e-Phenyl-3e-phenylthiocyclohexanone (**2e**)

To a mixture of **1a** (17 g)[9] and thiophenol (12 g) in chloroform (100 ml) was added a solution of triethylamine (1 ml) in chloroform and the resulting mixture stirred for 30 min at 25°, diluted with ether (50 ml) and washed successively with 5% aq. sodium hydroxide, water and saturated sodium chloride. The ethereal layer was dried (anhyd. Na_2SO_4) and solvent removed to give **2a**, yield 27 g (95%), m.p. 144° (from EtOH) (Found: C, 76.6; H, 6.4, S, 11.4. $C_{18}H_{18}OS$ requires C, 76.6; H, 6.4; S, 11.3%); PMR($CDCl_3$): 7.25 (*m*, 10H, Ar−*H*), 3.60 (*br*, 2H, C_2- and C_3-H), 1.50-2.60 (*m*, 6H, 4-, 5- and 6-methylene protons).

The oxime derivative (**3a**) had m.p. 185° (from EtOH) (Found: C, 72.7; H, 6.5; N, 4.8; S, 10.7. $C_{18}H_{19}NOS$ requires C, 72.7; H, 6.4; N, 4.7; S, 10.8%); PMR($CDCl_3$): 7.35 (*m*, 10H, Ar−*H*), 3.75 (*dt*, 1H, C_3−H), 8.20 (*br*, 1H, OH); 3.60 (*d*, 1H, C_2−H), 2.90 (*br*, *d*, 1H, C_6−eq. H), 1.50-2.50 (*m*, 5H, 4-CH_2, 5-CH_2 and C_6-ax. H).

The semicarbazone derivative (**4a**) had m.p. 198 (from EtOH) (Found: C, 67.3; H, 6.2; N, 12.8; S, 9.2. $C_{19}H_{21}N_3OS$ requires C, 67.3; H, 6.2; N, 12.4; S, 9.4%); PMR($CDCl_3$): 9.38 (*br*, 1H, NH), 7.30 (*m*, 10H, Ar−*H*), 5.53 (*br*, 2H, NH_2), 3.70 (*m*, 1H, C_3−H), 3.53 (*d*, 1H, C_2−H), 2.60 (*br d*, 1H, C_6−eq. H), 1.40-2.40 (*br*, 5H, 4-CH_2, 5-CH_2 and C_6−ax. H).

The hydrazone derivative (**5a**) had m.p. 105-7° (from EtOH) (Found: C, 76.6; H, 7.3; N, 4.7; S, 11.3. $C_{18}H_{20}N_2S$ requires C, 76.6; H; 7.1; N, 5.0; S, 11.1%); PMR($CDCl_3$): 7.35 (*m*, 10H, Ar−*H*), 5.05 (*br*, 2H, NH_2), 3.80 (*m*, 1H, C_3−H), 3.60 (*d*, 1H, C_2−H), 1.60-2.60 (*m*, 6H, 4-CH_2, 5-CH_2 and C_6-H).

2e-Phenyl-3e-phenylthiocyclohexanone 2,4-dinitrophenylhydrazone (**6a**)

To a suspension of 2,4-dinitrophenylhydrazine (1 g), in conc. H_2SO_4 (1 ml) was added cautiously. There after, a solution of **2a** (0.75 g) in methanol (15 ml) was added to the above mixture and warmed gently on a water-bath for 15 min. On cooling, the reaction mixture gave yellow crystals of **6a**, yield 0.78 g (65%), m.p. 134-35° (from EtOH) (Found: C, 62.4; H, 4.7; N, 12.2; S, 6.9. $C_{24}H_{22}N_4S$ requires C, 62.3; H, 4.8; N, 12.1; S, 6.9%); PMR($CDCl_3$): 11.30 (*br*, 1H, NH), 9.65 (*d*, 1H, C_3−H of phenyl attached to nitrogen), 8.15 (*d*, 1H, C_5−H of phenyl attached to nitrogen), 7.50 (*d*, 1H, C_6−H of phenyl attached to nitrogen), 7.20 (*m*, 10H, Ar−*H*), 3.80 (*br*, 2H, C_2− and C_3−H); 1.50-2.50 (*m*, 6H, 4-, and 6-CH_2).

The filtrate from the above crystallisation was concentrated to half of the volume which on cooling gave red crystals of 2-phenyl-2-cyclohexen-1-one 2,4-dinitrophenylhydrazone (**7a**) (0.1 g, 15%), m.p. 162° (lit.[11], m.p. 163-4°) (from EtOH).

Hydrolysis of 2e-phenyl-3e-phenylthiocyclohexanone semicarbazone (**4a**)

The semicarbazone **4a** (1 g) was suspended in a solution of oxalic acid (1 g) in water (20 ml) and refluxed for 20 min. The mixture was cooled, diluted and filtered to give 2*e*-phenyl-3*e*-phenylthiocyclohexanone (**2a**) (0.75 g, 90%), m.p. 144° (from EtOH).

1e-Hydroxy-2e-phenyl-3e-phenylthiocyclohexane (**8a**)

Sodium borohydride as well as lithium aluminium hydride reduction of the ketone **2a** (1 g) was carried out by the usual procedures. In both the cases, the same alcohol 1*e*-hydroxy-2*e*-phenyl-3*e*-phenylthiocyclohexane was obtained as a single entity, yield 0.9 g (90%). m.p. 117-18° (from EtOH) (Found: C, 75.9; H, 7.0; S, 11.20. $C_{18}H_{20}OS$ requires C, 76.1; H, 7.0; S, 11.3%): PMR($CDCl_3$): 7.30 (*d*, 10H, Ar−*H*), 3.70 (*t*, *d*, 1H, C_3−H), 3.25 (*t*, *d*, 1H, C_1−H), 1.55 (*d*, 1H, OH), 2.45 (*dd*, 1H, C_2−H), 1.30-2.30 (*m*, 6H, 4-CH_2, 5-CH_2 and 6-CH_2).

Oxidation of 1e-hydroxy-2e-phenyl-3e-phenylthiocyclohexane (**8a**)

A solution of **8a** (1 g) in dioxane (10 ml) was treated with potassium dichromate (0.5 g) in 5% sulphuric acid (10 ml) and warmed on a water-bath for 15 min at 60°. The mixture was then diluted and extracted with ether. The ethereal layer after successive washings with saturated sodium sulphate was evaporated to give **2a**, yield 0.4 g (66%), m.p. and m.m.p. 95°.

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Aromatic Benzylation: Part IV—Synthesis of Nuclear Benzylated Isoflavones & Flavones

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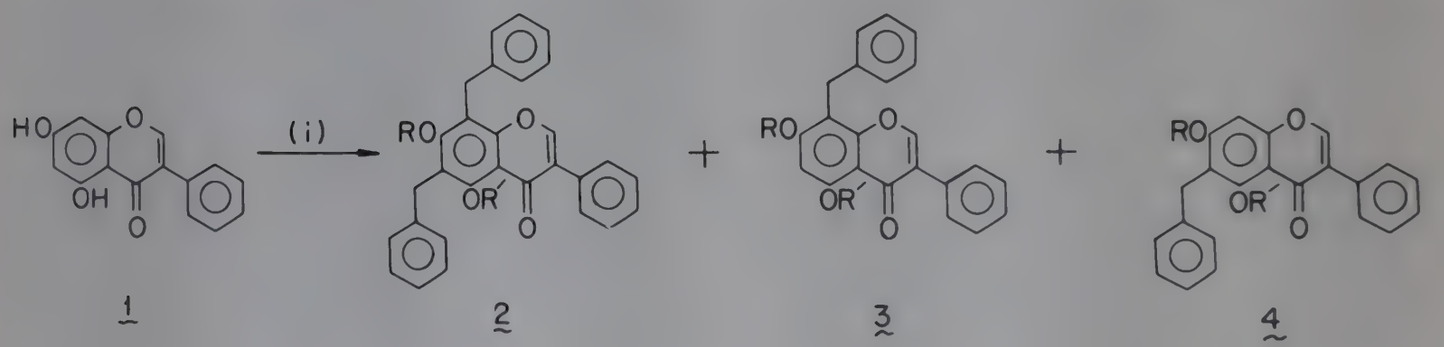
5,7-Dihydroxyisoflavone (**1**) on reaction with benzyl alcohol in the presence of boron trifluoride etherate and dioxan gives 6-C-benzyl (**4a**), 8-C-benzyl (**3a**) and 6,8-di-C-benzyl (**2a**) derivatives. Parallel reaction with 3-O-methylgalangin (**5**) furnishes **6a**, **7a** and **8a**. Mono-C-benzyl derivatives in both cases have been differentiated by comparing their PMR data with those of acetates.

In continuation of our work[1-3] on the synthesis of C-benzylated flavonoids, aromatic benzylation has now been studied on 5,7-dihydroxyisoflavone[4] (**1**) and 3-O-methylgalangin (**5**). When these were reacted with benzyl alcohol in the presence of boron trifluoride etherate and dioxan, a mixture of three products was obtained in each case. The isoflavone afforded 6-C-benzyl- (**4a**; 34%)-, 8-C-benzyl- (**3a**; 21%)- and 6,8-di-C-benzyl- (**2a**; 8%)-5,7-dihydroxyisoflavones, whereas the flavone **5** gave 6,8-di-C-benzyl-(**6a**; 9%)-, 8-C-benzyl- (**7a**; 20%)- and 6-C-benzyl-(**8a**; 32%)- 5,7-dihydroxy-3-methoxyflavones. The C-benzyl group in the above monobenzyl derivatives was located by comparing the downfield shifts of the aromatic proton of ring-A on acetylation as reported earlier[1]. Thus, the greater downfield shift (Δ_δ 0.85 or 0.75), experienced on acetylation showed the presence of C_6-H and the smaller shift (Δ_δ 0.67 or 0.26) C_8-H. Hence, the



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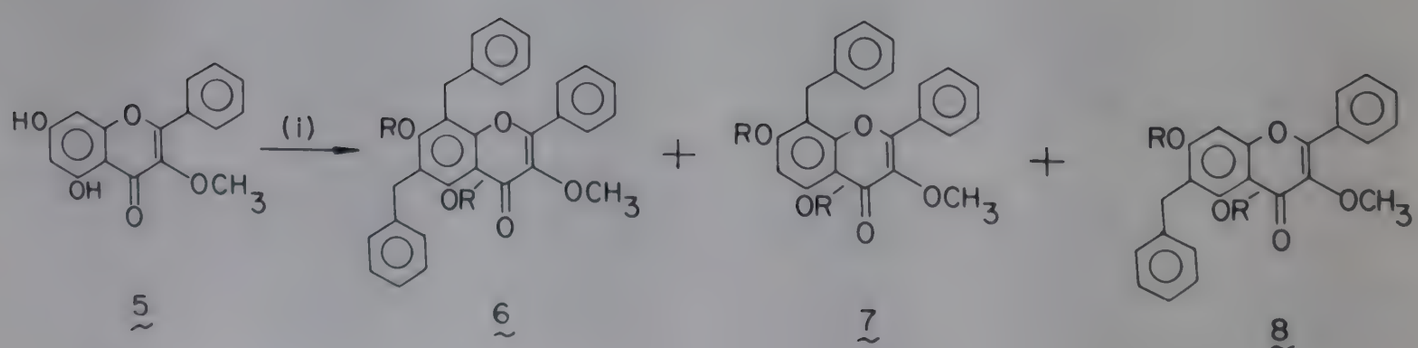

5 6 7 8

For 2-4 & 6-8: a, R = R′ = H; b, R = R′ = $COCH_3$; c, R = $COCH_3$, R′ = H; d, R = Me, R′ = H

Reagents(i): $PhCH_2OH$, BF_3–Et_2O,

aromatic benzylation can conveniently be carried out in flavonols and isoflavones having phloroglucinol system with benzyl alcohol.

Experimental Procedure

Unless stated otherwise, all m.ps are uncorrected; pet. ether had boiling range of 60-80°; R_f values refer to TLC; silica gel G was used for column chromatography and TLC; solvent systems used for TLC were: (A) benzene-ethyl acetate (19 : 1) and (B) benzene-ethyl acetate (9 : 1); UV spectra were recorded in methanol on a Perkin-Elmer 554 spectrophotometer (λ_{max} in nm, logε values in parentheses); IR spectra were measured using KBr disc on a Perkin-Elmer infrared spectrophotometer (ν_{max} in cm^{-1}); PMR spectra were recorded in $CDCl_3$ on a Perkin-Elmer R-32 (90 MHz) spectrometer using TMS as internal standard (chemical shifts in δ ppm, J values in Hz).

Reaction of 5,7-*dihydroxyisoflavone* (**1**) *and* 3-*O*-*methyl-galangin* (**5**) *with benzyl alcohol*

To a solution of **1** or **5** (9.6 mmol) in dry dioxan (150 ml) was added a solution of freshly distilled benzyl alcohol (1.1 ml, 9.6 mmol) in dioxan (25 ml), followed by borontrifluoride etherate (15 ml). The resulting solution was stirred for 10 hr at 40-45° in the case of **1** and for 4 hr at 60-70° in the case of **5**, cooled and diluted with ether (500 ml). The ethereal layer was washed with water, dried (Na_2SO_4), evaporated to dryness and the residue on purification by column chromatography furnished the following compounds (for PMR spectra see Table 1).

From **1**[4]

Fraction-A—It crystallised from pet. ether-benzene to give 6,8-*di-C-benzyl*-5,7-*dihydroxyisoflavone* (**2a**) as colourless plates (300 mg), m.p. 144-45°; gave brown Fe^{3+} reaction; R_f 0.90 (solvent A) (Found: C, 80.4; H, 5.3. $C_{29}H_{22}O_4$ requires C, 80.2; H, 5.1%); UV: 290 (3.79), 262 (4.17) and 204 (4.47); IR: 3421, 1660, 1629, 1575, 1490, 1460, 1385, 1212 and 1090.

The diacetate (**2b**), prepared by acetic anhydride-pyridine method, crystallised from methanol as colourless plates, m.p. 132-33°; R_f 0.90 (solvent B) (Found: C, 76.5; H, 5.4. $C_{33}H_{26}O_6$ requires: C, 76.4; H, 5.1%).

Fraction-B—It crystallised from benzene to give 8-C-benzyl-5,7-dihydroxyisoflavone (**3a**) as colourless crystals (600 mg), m.p. 194-95°; gave greenish-violet ferric reaction; R_f 0.68 (solvent A) (Found: C, 77.0; H,

Table 1—PMR Data of C-Benzylated Isoflavones (**2-4**) and Flavonols (**6-8**) (Chemical shifts in δ, ppm)

Compd	$-OCOCH_3$ (*s*)	$-OCH_3$ (*s*)	$-CH_2Ph$ (*s*)	C_6-H (*s*)	C_8-H (*s*)	C_6H_5 (*bm*)	C_2-H (*s*)	Chelated OH (*s*)
2a	—	—	3.98 (4H)	—	—	7.22 (15H)	7.75	13.60
2b	2.04 and 2.26 (3H each)	—	3.86 and 4.00 (2H each)	—	—	7.73 (15H)	7.72	—
3d	—	3.45 (3H)	4.90 and 4.0 (2H each)	—	—	7.10 (15H)	7.55	13.20
3a	—	—	3.95 (2H)	6.25	—	7.10 (10H)	7.66	13.50
3b	2.12 and 2.36 (3H each)	—	3.93 (2H)	7.10	—	7.26 (10H)	7.79	—
4a	—	—	4.03 (2H)	—	6.41	7.27 (10H)	7.84	13.42
4b	2.10 and 2.34 (3H each)	—	3.91 (2H)	—	7.08	7.27 (10H)	7.80	—
6a*	—	3.88 (3H)	4.12 and 4.20 (2H each)	—	—	7.58 (15H)	—	13.04
6d	—	3.60 and 3.84 (3H each)	4.12 and 4.20 (2H each)	—	—	7.38 (15H)	—	12.88
6c	2.12 (3H)	3.81 (3H)	3.94 and 4.01 (2H each)	—	—	7.43 (15H)	—	12.95
7a	—	3.62 (3H)	3.95 (2H)	6.41	—	7.57 (10H)	—	—
7b	2.08 and 2.36 (2s, 3H each)	3.81 (3H)	3.97 (2H)	7.33	—	7.69 (10H)	—	—
7d	—	3.85 and 3.89 (3H each)	4.02 (2H)	6.46	—	7.56 (10H)	—	12.76
8a	—	3.68 (3H)	4.14 (2H)	—	6.64	7.52 (10H)	—	12.75
8b	2.25 and 2.46 (3H each)	3.77 (3H)	4.20 (2H)	—	6.90	7.42 (10H)	—	
8d	—	3.90 and 3.94 (3H each)	4.16 (2H)	—	6.44	7.47 (10H)	—	13.94

*PMR spectrum was recorded in $CDCl_3$ containing a few drops of TFA.

4.6. $C_{22}H_{16}O_4$ requires: C, 76.7; H, 4.7%); UV: 299 (3.77), 259 (4.39) and 210 (4.30); IR: 3420, 3220, 1650, 1615, 1520, 1480, 1465 and 1315.

Its diacetate (**3b**) crystallised from methanol as colourless plates, m.p. 173-74°; R_f 0.65 (solvent B) (Found: C, 72.8; H, 4.6. $C_{26}H_{20}O_6$ requires C, 72.9; H, 4.7%).

Fraction-C—It crystallised from benzene-pet. ether to give 6-C-benzyl-5,7-dihydroxyisoflavone (**4a**) as pale yellow plates (1.0 g), m.p. 224-25°; gave greenish-violet ferric reaction, R_f 0.51 (solvent A) (Found: C, 76.6; H, 4.7. $C_{22}H_{16}O_4$ requires C, 76.7; H, 4.7%); UV: 300 (3.74), 258 (4.37) and 208 (4.29); IR: 3440, 3300, 1630, 1610, 1575, 1500, 1460, 1425 and 1370.

Its diacetate (**4b**) crystallised from methanol as colourless plates, m.p. 193-94°; R_f 0.42 (solvent B) (Found: C, 72.7; H, 4.8. $C_{26}H_{20}O_6$ requires C, 72.9; H, 4.7%).

Fraction-D—It crystallised from benzene to afford 5,7-dihydroxyisoflavone (**1**) (300 mg), m.p. 195-96° (lit.[4], m.p.196-97°).

From **5**[5]

Fraction-E—It crystallised from pet. ether to give 6,8-di-C-benzyl-5,7-dihydroxy-3-methoxyflavone (**6a**) as glistening yellow needles (400 mg), m.p. 170-71°; gave greenish-violet ferric reaction; R_f 0.79 (solvent A) (Found: C, 77.3; H, 5.3. $C_{30}H_{24}O_5$ requires C, 77.6; H, 5.2%); UV: 361 (3.97), 323 (4.37) and 225 (4.36); IR: 3420, 3060, 1650, 1625, 1580, 1500, 1480 and 1375.

The monoacetate (**6c**), prepared by acetic anhydride-pyridine method at room temperature, crystallised from methanol as colourless needles, m.p. 140-41°; gave brown ferric reaction; R_f 0.75 (solvent A) (Found: C, 75.7; H, 5.2. $C_{32}H_{26}O_6$ requires C, 75.9; H, 5.2%).

Fraction-F—It crystallised from benzene-pet. ether to give 8-C-benzyl-5,7-dihydroxy-3-methoxyflavone (**7a**) (800 mg), m.p. 218-19°; gave greenish-violet ferric reaction; R_f 0.62 (solvent A) (Found: C, 73.7; H, 5.0. $C_{23}H_{18}O_5$ requires C, 73.8; H, 4.9%); UV: 361 (3.69), 322 (3.95) and 277 (4.31); IR: 3420, 3080, 1030, 1615, 1575, 1480, 1370, 1318 and 1228.

Its diacetate (**7b**) crystallised from methanol as colourless plates, m.p. 160-61°; R_f 0.54 (solvent B) (Found: C, 70.4; H, 4.9. $C_{27}H_{22}O_7$ requires C, 70.7; H, 4.8%).

Fraction-G—It crystallised from benzene-pet. ether to give 6-C-benzyl-5,7-dihydroxy-3-methoxyflavone (**8a**) as light yellow shining plates (1.0g), m.p. 175-76°; gave greenish violet ferric reaction; R_f 0.42 (solvent A) (Found: C, 73.6; H, 4.9. $C_{23}H_{18}O_5$ requires C, 73.8; H, 4.9%); UV: 358 (3.92), 322 (3.92), 276 (4.52) and 218 (4.01); IR: 3420, 3240, 1658, 1620, 1580, 1510 and 1460.

Its acetate (**8b**) crystallised from methaol as colourless plates, m.p. 130-31°; R_f 0.37 (solvent A) (Found: C, 70.6; H, 5.1. $C_{27}H_{22}O_7$ requires C, 70.7; H, 4.8%).

Fraction-H—It crystallised from ethyl acetate to give the starting material (**5**; 400 mg), m.p. 296-97° (lit.[5], m.p. 298-99°).

Partial methylation of **2a**, **6a**, **7a**, **8a**

The substrate (1 mmol) in dry acetone (10 ml) was refluxed with Me_2SO_4 (0.1 ml, 1 mmol) and freshly ignited K_2CO_3 (200 mg) for 0.5 hr. The products were crystallised from pet. ether or benzene-pet. ether. Their data are as follows:

6,8-*Di-C-benzyl-5-hydroxy-7-methoxyisoflavone* (**2d**): m.p. 126-27°; gave brown ferric reaction; R_f 0.78 (solvent B) (Found: C, 80.7; H, 5.3. $C_{30}H_{24}O_4$ requires C, 80.4; H, 5.4%).

6,8-*Di-C-benzyl-5-hydroxy-3,7-dimethoxyflavone* (**d**): m.p. 112-13°; gave brown ferric reaction; R_f 0.61 (solvent A) (Found: C, 77.5; H, 5.6. $C_{31}H_{26}O_5$ requires C, 77.8; H, 5.5%).

8-*C-Benzyl-5-hydroxy-3,7-dimethoxyflavone* (**7d**): m.p. 80-81°; gave brown ferric reaction; R_f 0.58 (solvent B) (Found: C, 74.0; H, 5.0. $C_{24}H_{20}O_5$ requires C, 74.2; H, 5.2%).

6-*C-Benzyl-5-hydroxy-3,7-dimethoxyflavone* (**8d**): m.p. 158-59°; gave brown ferric reaction; R_f 0.49 (solvent B) (Found C, 74.1; H, 5.2. $C_{24}H_{20}O_5$ requires C, 74.2; H, 5.2%).

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Hansch Analysis of Antineoplastic Agents, 5-N-Substituted-2-*p*-substituted-benzenesulphonyl-L-glutamines

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Partition coefficients (*P*) of some antineoplastic 5-N-substituted-2-*p*-substituted-benzenesulphonyl-L-glutamines (I) have been determined experimentally and an attempt has been made to correlate antineoplastic activity with $\Sigma\pi$, log *P*, $\pi_{Aromatic}$, $\pi_{Aliphatic}$, etc. Excellent correlations are obtained with $\pi_{Aliphatic}$ and $\Sigma\pi$ in addition to log *P*.

The title investigation is a part of our broad programme concerning rational drug design of potential antineoplastic agents. These glutamine analogs are expected to show antineoplastic activity by way of glutamine and/or folic acid antagonism[1]. The rationale for investigating these compounds has been described earlier[2-11].

Synthesis of these compounds (I) have been earlier reported from this laboratory[10], and these show appreciable antineoplastic activity[10]. The present paper covers determination of partition coefficient (*P*) and log *P* values of compounds (I) and attempts to correlate antineoplastic activity of I with log *P*. A comparison of $\Sigma\pi$ and log *P* in Hansch analysis of these compounds (I) has also been made. Since log *P* is non-additive in I, attempts have been made to correlate antineoplastic activity and low *P* with $\pi_{Aromatic}$, $\pi_{Aliphatic}$ and $\Sigma\pi$ (ref.12,13).

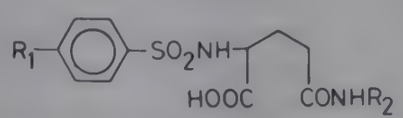
Materials and Methods

Partition coefficient

Partition coefficients were determined following Hansch procedure[14,15], as earlier reported from this laboratory[16,17], *n*-octanol saturated with water and water saturated with *n*-octanol were used as the partition systems[18].

Stock solutions of I of concentration about 20 mg/100 ml were accurately prepared in water and diluted ten-fold with water to make the standard solutions. The maximum absorptions of standard solutions were obtained using a Beckman, model M-25, double beam digital spectrophotometer. Compounds (**1a-4a**) exhibited λ_{max} at 225 ($E_1^{1\%}$ cm = 369.2946), 223 (308.1896), 226 (273.7903) and 228 (401.8691), respectively while **1b-4b** exhibited λ_{max} at 233 ($E_1^{1\%}$ cm = 407.5829), 233 (359.4470), 233 (333.3333) and 234 (313.9013) respectively.

From the concentrations of stock and standard solutions and absorbances of standard solutions and partitioned aqueous layers, partition coefficient (*P*) and log *P* values were calculated. The P-values for **1a-4a, 1b-4b** were found to be 3.7823, 2.4450, 0.8235, 0.6872, 1.3507, 1.0442, 8.2232 and 2.0689, respectively.



(I)

(a) R_1 = H : (I) R_2 = H (1), C_2H_5 (2), n-C_3H_7 (3), n-C_5H_{11} (4).

(b) R_1 = CH_3 : (II) R_2 = n-C_3H_7 (1), n-C_4H_9 (2), n-C_6H_{13} (3), cyclohexyl (4).

Results

Hansch analysis : Set I

Herein Eqs.(1-12) were utilised to find out the extent of dependence of antineoplastic activity of I on the partition coefficient (*P*), electronic parameter (σ), steric parameter (E_s) as well as comparison of that with hydrophobic parameter (π) where hydrophobic parameter ($\Sigma\pi$) was used instead of log *P*.

$$Y = K_1X + K_2 \quad \ldots (1)$$

$$Y = K_1X^2 + K_2X + K_3 \quad \ldots (2)$$

$$Y = K_1X + K_2(\Sigma\sigma) + K_3 \quad \ldots (3)$$

$$Y = K_1X + K_2(\Sigma Es) + K_3 \quad \ldots (4)$$

$$Y = K_1X^2 + K_2X + K_3(\Sigma\sigma) + K_4 \quad \ldots (5)$$

$$Y = K_1X^2 + K_2X + K_3(\Sigma Es) + K_4 \quad \ldots (6)$$

$$Y = K_1X + K_2(\Sigma\sigma) + K_3(\Sigma Es) + K_4 \quad \ldots (7)$$

$$Y = K_1X + K_2(\Sigma\sigma) + K_3\sigma_1 + K_4 \quad \ldots (8)$$

$$Y = K_1X^2 + K_2X + K_3(\Sigma\sigma) + K_4(\Sigma Es) + K_5 \quad \ldots (9)$$

$$Y = K_1X^2 + K_2X + K_3(\Sigma\sigma) + K_4\sigma_1 + K_5 \quad \ldots (10)$$

$$Y = K_1X + K_2(\Sigma\sigma) + K_3(\Sigma Es) + K_4\sigma_1 + K_5 \quad \ldots (11)$$

$$Y = K_1X^2 + K_2X + K_3(\Sigma\sigma) + K_4(\Sigma Es) + K_5\sigma_1 + K_6 \quad \ldots (12)$$

where $X = \Sigma\pi$ or log P.

As both the parameters $\Sigma\pi$ and log P were utilized for correlation, and altogether eight compounds were investigated, a total number of 24 (i.e. 12 + 12) types of equations, each type in its turn containing eight simultaneous equations representing the eight compounds were solved by the computer.

As such 24 runs were fed in the computer and a total number of 192 (i.e., 8×24) equations were handled in Set I. Logarithms of antineoplastic activity and all the parameters are recorded in Table 1.

Least square solution of these types of simultaneous equations with the help of Boroughs B6700 computer gave best fitting equations. These along with the standard deviations (S) and multiple correlation coefficients (R) are recorded in Table 2.

Set II

Here attempts were made to correlate antineoplastic activity with parameters generated from aromatic substitutions only, e.g. $\pi_{Aromatic}$, $\sigma_{Aromatic}$ in addition to log P. Inclusion of these parameters led to 21 types of equations in this set instead of just 12 types in Set I. Out of 21 runs, only two (i.e. runs 13 and 14) showed better correlations than the best correlation obtained in Set I i.e., run 12_b of Table 2. These along with S and R are recorded in Table 3.

Set III

Similarly, attempts were made to correlate antineoplastic activity with parameters generated from aliphatic substitutions only, e.g. $\pi_{Aliphatic}$, $\sigma_{Aliphatic}$ etc. and log P. Here, 66 types of equations of which 24 (i.e. runs 15-38) showed better correlations than run 12_b of Table 2. These are recorded in Table 4.

Set IV

In this set correlation was sought amongst antineoplastic activity and parameters generated from both aromatic and aliphatic substitutions as well as log P. Inclusion of all these parameters resulted in 43 types of equations of which 23 runs (39-61) showed better correlations than run 12_b in Table 2. These are shown with S and R as Set IV in Table 5.

Set V

Finally, attempts were made to correlate antineoplastic activity with both log P and $\Sigma\pi$, as nonadditive log P values of the compounds investigated encouraged us to search for such correlations. In this set, 51 types of equations resulted, of which 29 runs (62-90) showed better correlations than run 12_b of Table 2. These are recorded in Table 6.

Discussion

Predicted antineoplastic activities, on the basis of the best correlations obtained in each set (i.e. run 12_b of Set I, run 14 of Set II, run 35 of Set III, run 61 of Set IV

Table 1 — Log of Antineoplastic Activity with Various Parameters of 5-N-Substituted-2-*p*-substituted-benzenesulphonyl-L-glutamines (I)

Compd	Log % inhibition of tumor wt	π_{Ali} ($=\pi_{R_2}$)	σ_{Ali} ($=\sigma_{R_2}$)	E^*_{sAli} ($=E_{sR_2}$)	σ_1	$\Sigma\pi^{2\dagger}$ ($=\pi_{Aro}+\pi_{Ali}$)	$\Sigma\sigma$ ($=\sigma_{Aro}+\sigma_{Ali}$)	log $P^{2\ddagger}$
1a	1.8426	0.00	0.4900	1.240	0.00	0.0000	0.490	0.3337
2a	1.8506	1.00	-0.1000	-0.070	-0.05	1.0000	-0.100	0.1508
3a	1.9031	1.50	-0.1150	-0.360	-0.03	2.2500	-0.115	0.0072
4a	1.7853	2.50	-0.2300	-0.400	-0.04	6.2500	-0.230	0.0265
1b	1.8261	1.50	0.1150	-0.360	-0.03	4.0804	-0.285	0.0170
2b	1.6803	2.00	-0.1300	-0.390	-0.04	6.3504	-0.300	0.0003
3b	1.8751	3.00	-0.2500	-0.400	-0.04	12.3904	-0.420	0.8374
4b	1.6618	2.51	-0.1800	-0.790	-0.02	9.1809	-0.350	0.0997

π_{Aro} ($=\pi_{R_1}$): **1a-4a**, 0.0000; **1b-4b**, 0.5200; σ_{Aro} ($=\sigma_{R_1}$): **1a-4a** = 0.0000; **1b-4b**, -0.1700

E_{sAro} ($=E_{sR_1}$): **1a-4a** and **1b-4b**, 0.0000

*Since, E_{sAro} = 0.0000, E_{sAli} values also represent ΣE_s

†$(\Sigma\pi)^2$ values

‡$(\log P)^2$ values

Table 2—Relation between Antineoplastic Activity and $\Sigma\pi$ and that of log P (Set I) and a Comparison between them in Hansch Analysis of I with Standard Deviation (S) and Multiple Correlation Coefficient (R)

Run No.	Governing equation (Y =)	S	R	Run No.	Governing equation (Y =)	S	R
1_a	$-0.0312\ (\Sigma\pi) + 1.8658$	0.0876	0.4022	1_b	$0.0625 \log P + 1.7865$	0.0925	0.2561
a_a	$0.0066\ (\Sigma\pi)^2 - 0.0544\ (\Sigma\pi) + 1.8783$	0.0954	0.4130	2_b	$0.2519\ (\log P)^2 - 0.1178 \log P + 1.7876$	0.0946	0.4294
3_a	$-0.0505\ (\Sigma\pi) + 0.0849\ (\Sigma\sigma) + 1.8907$	0.0952	0.4176	3_b	$0.0530 \log P + 0.0902\ (\Sigma\sigma) + 1.8040$	0.0967	0.3857
4_a	$-0.0240\ (\Sigma\pi) + 0.0162\ (\Sigma E_s) + 1.8545$	0.0957	0.4070	4_b	$0.0366 \log P + 0.0462\ (\Sigma E_s) + 1.8023$	0.0963	0.3947
5_a	$0.0404\ (\Sigma\pi)^2 - 0.2739\ (\Sigma\pi) - 0.4406\ (\Sigma\sigma) + 2.0723$	0.0993	0.5308	5_b	$0.3593\ (\log P)^2 - 0.2095 \log P + 0.1405\ (\Sigma\sigma) + 1.8149$	0.0934	0.6038
6_a	$0.0121\ (\Sigma\pi)^2 - 0.0843\ (\Sigma\pi) - 0.0233\ (\Sigma E_s) + 1.9051$	0.1068	0.4152	6_b	$0.3238\ (\log P)^2 - 0.2043 \log P + 0.0627\ (\Sigma E_s) + 1.8091$	0.0951	0.5834
7_a	$-0.0686\ (\Sigma\pi) - 0.4555\ (\Sigma\sigma) + 0.1500\ (\Sigma E_s) + 1.8952$	0.1003	0.5157	7_b	$0.0341 \log P - 0.0153\ (\Sigma\sigma) + 0.0535\ (\Sigma E_s) + 1.8019$	0.1076	0.3946
8_a	$-0.0162\ (\Sigma\pi) + 0.1303\ (\Sigma\sigma) 2.4448\ \sigma_1 + 1.7808$	0.1021	0.4904	8_b	$0.0670 \log P + 0.2030\ (\Sigma\sigma) + 3.1282\ \sigma_1 + 1.7210$	0.0974	0.5550
9_a	$0.0281\ (\Sigma\pi)^2 - 0.2610\ (\Sigma\pi) - 0.5351\ (\Sigma\sigma) + 0.0820\ (\Sigma E_s) + 2.0196$	0.1132	0.5469	9_b	$0.3803\ (\log P)^2 - 0.2066 \log P + 0.2457\ (\Sigma\sigma) - 0.0519\ (\Sigma E_s) + 1.8176$	0.1073	0.6086
10_a	$0.0362\ (\Sigma\pi)^2 - 0.2228\ (\Sigma\pi) - 0.2286\ (\Sigma\sigma) - 1.9894\ \sigma_1 + 1.9638$	0.1112	0.5695	10_b	$0.3183\ (\log P)^2 - 0.1678 \log P + 0.2290\ (\Sigma\sigma) - 2.6152\ \sigma_1 + 1.7443$	0.0982	0.6878
11_a	$-0.0433\ (\Sigma\pi) - 0.2412\ (\Sigma\sigma) + 0.1177\ (\Sigma E_s) - 1.5283\ \sigma_1 + 1.8254$	0.1141	0.5362	11_b	$0.0788 \log P + 0.2710\ (\Sigma\sigma) + 0.0322\ (\Sigma E_s) - 3.25549\ \sigma_1 + 1.7189$	0.1123	0.5571
12_a	$0.0310\ (\Sigma\pi)^2 - 0.2020\ (\Sigma\pi) - 0.2963\ (\Sigma\sigma) + 0.0376\ (\Sigma E_s) - 1.7610\ \sigma_1 + 1.9520$	0.1358	0.5722	12_b	$0.3629\ (\log P)^2 - 0.1538 \log P + 0.5015\ (\Sigma\sigma) - 0.1272\ (\Sigma E_s) - 3.0443\ \sigma_1 + 1.7393$	0.1165	0.7108

Table 3— Runs Showing Better Correlations (with S and R values) of Set II than Run 12_b in Table 2

Run No	Governing equation (Y =)	S	R
13	$0.2339\ (\log P)^2 - 0.0696 \log P + 0.5798\ \sigma_{Aro} + 1.8276$	0.0814	0.7189
14	$0.0987 \log P - 5.000\ \Sigma_{Aro}^2 - 7.0000\ \sigma_{Aro} + 1.8582$	0.0738	0.7764

and run 73 of Set V) are recorded in Table 7 to facilitate comparison of results.

Hansch analysis using $\Sigma\pi$ did not show any appreciable correlation, but the use of log P instead of $\Sigma\pi$ led to appreciable correlation. This indicates that log P has greater importance in antineoplastic activity than $\Sigma\pi$.

When correlation was sought amongst antineoplastic activity (log P) and parameters generated from aromatic substitutions only (Set II), correlation did not improve much. This suggests that aromatic substitution alone does not very much affect antineoplastic activity. Whereas good correlation was obtained amongst antineoplastic activity, (log P) and parameters generated from aliphatic substitutions only (Set III), indicating that aliphatic substitution is much more important for antineoplastic activity in I than the aromatic substitution.

The above correlation remained the same when log P and parameters generated from both aromatic and aliphatic substitutions (Set IV) were used supporting the hypothesis than aliphatic substitutions have greater role than aromatic substitutions.

Lastly, the use of both log P and $\Sigma\pi$ together along with the other parameters (Set V) resulted in an excellent correlation signifying the importance of log P and $\Sigma\pi$ in this class of compounds.

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Table 4— Relationship Between log P and Parameters Generated from Aliphatic Substituent (Set III) with S and R values

Run No	Governing equation (Y =)	S	R
15	0.7068 (log P)^2 - 0.3936 log P - 0.0282 π^2_{Ali} + 1.8858	0.0621	0.8480
16	0.5846 (log P)^2 - 0.3598 log P - 0.0722 π_{Ali} + 1.9164	0.0744	0.7722
17	0.8142 (log P)^2 - 0.3804 log P - 0.0749 π^2_{Ali} + 0.1400 π_{Ali} + 1.7986	0.0597	0.8972
18	0.8011 (log P)^2 - 0.4095 log P - 0.0330 π^2_{Ali} - 0.2564 σ_{Ali} + 1.9426	0.0586	0.9014
19	0.9252 (log P)^2 - 0.4543 log P - 0.0492 π^2_{Ali} - 0.1044 Es_{Ali} + 1.9231	0.0512	0.9256
20	0.5246 (log P)^2 - 0.2898 log P - 0.7711 σ_{Ali} + 0.1907 Es_{Ali} + 1.9742	0.0776	0.8186
21	0.788 (log P)^2 - 0.4323 log P - 0.1097 π_{Ali} - 0.4478 σ_{Ali} + 2.0536	0.0580	0.9035
22	1.0435 (log P)^2 - 0.5614 log P - 0.2322 π_{Ali} - 0.2421 Es_{Ali} + 2.1186	0.0415	0.9517
23	0.3497 (log P)^2 - 0.1205 π^2_{Ali} + 0.3884 π_{Ali} + 0.1435 Es_{Ali} + 1.5538	0.0916	0.7359
24	0.6349 (log p)^2 - 0.3131 π^2_{Ali} + 0.9529 π_{Ali} + 1.4210 σ_{Ali} + 0.9467	0.0849	0.7787
25	0.7843 (log P)^2 - 0.4680 log P + 0.0543 π^2_{Ali} - 0.2896 π_{Ali} + 2.2349	0.0705	0.9049
26	1.1400 (log P)^2 - 0.6896 log P + 0.0614 π^2_{Ali} - 0.5054 π_{Ali} - 0.3924 Es_{Ali} + 2.3406	0.0448	0.9627
27	1.1579 (log P)^2 - 0.5492 log P - 0.0842 π^2_{Ali} + 0.7452 σ_{Ali} - 0.3467 Es_{Ali} + 1.84444	0.0512	0.9511
28	0.8886 (log P)^2 - 0.4556 log P - 0.0337 π^2_{Ali} - 0.4217 σ_{Ali} + 1.5330 σ_I + 2.0227	0.0679	0.9122
29	1.1563 (log P)^2 - 0.6233 log P - 0.2959 π_{Ali} + 0.3253 σ_{Ali} - 0.3798 Es_{Ali} + 2.1339	0.0463	0.9601
30	0.8890 (log P)^2 - 0.4862 log P - 0.1130 π_{Ali} - 0.6410 σ_{Ali} + 1.7299 σ_I + 2.1479	0.0660	0.9172
31	0.6594 (log P)^2 - 0.3244 π^2_{Ali} + 0.9758 π_{Ali} + 1.5516 σ_{Ali} - 0.0311 Es_{Ali} + 0.9135	0.1038	0.7793
32	0.6155 (log P^2 - 0.3172 π^2_{Ali} + 0.9642 π_{Ali} + 1.5869 σ_{Ali} - 1.3906 σ_I + 0.8698	0.1013	0.7913
33	1.1263 (log P)^2 - 0.6796 log P + 0 0810 π^2_{Ali} - 0.5673 π_{Ali} - 0.1280 σ_{Ali} - 0.3860 Es_{Ali} + 2.4053	0.0633	0.9629

(*Contd.*)

Table 4— Relationship Between log P and Parameters Generated from Aliphatic Substituent (Set III) with S and R values-*Contd.*

Run No	Governing equation (Y =)	S	R
34	0.8618 (log P)^2 - 06706 log P + 0.2222 π^2_{Ali} - 0.8517 π_{Ali} - 2.0574 σ_{Ali} + 2.9629 σ_I + 2.9562	0.0849	0.9320
35	1.4111 (log P)^2 - 0.5971 log P - 0.1714 π^2_{Ali} - 3.2293 σ_{Ali} - 0.9595 Es_{Ali} - 6.6199 σ_I + 1.3249	0.0310	0.9912.
36	1.2547 (log P)^2 - 0.6708 log P - 0.4475 π_{Ali} + 1.3959 σ_{Ali} - 0.7030 Es_{Ali} - 3.6949 σ_I + 2.0009	0.0477	0.9791
37	1.7607 (log P)^2 - 1.0006 π^2_{Ali} + 2.3913 π_{Ali} + 10.9249 σ_{Ali} - 1.7535 Es_{Ali} - 18.0621 σ_I - 1.9235	0.0668	0.9585
38	-0.6282 log P + 0.7113 π^2_{Ali} - 2.0691 π_{Ali} - 7.1549 σ_{Ali} + 0.7976 Es_{Ali} + 0.9892 σ_I + 4.7322	0.1572	0.7416

Table 5— Runs Showing Better Correlations (S and R values) of Set IV than Run 12_b of Set I

Run No	Governing equation (Y =)	S	R
39	0.6438 (log P)^2 - 0.3465 log P - 0.0864 π^2_{Aro} - 0.0246 π^2_{Ali} + 1.8826	0.1863	0.8538
40	0.7913 (log P)^2 - 0.2783 log P - 0.0739 π^2_{Aro} + 0.0535 π_{Ali} + 1.8986	0.2208	0.7869
41	0.2197 (log P)^2 - 0.0552 log P + 0.6027 σ_{Aro} - 0.0169 Es_{Ali} + 1.8270	0.2485	0.7196
42	0.1895 (log P)^2 - 0.2918 π^2_{Aro} - 0.0087 π^2_{Ali} + 1.8416	0.2061	0.7469
43	0.1607 (log P)^2 - 0.1696 π_{Aro} - 0.0139 π_{Ali} + 1.8419	0.2152	0.7198
44	0.2024 log P - 0.5039 π^2_{Aro} - 0.0477 π^2_{Ali} + 0.0088 π_{Aro} + 0.1568 π_{Ali} + 1.7263	0.3075	0.7126
45	0.1113 log P - 0.4505 π^2_{Aro} - 0.0130 π^2_{Ali} - 0.3155 σ_{Aro} - 0.5389 σ_{Ali} + 0.1578 Es_{Ali} + 1.8461	0.4037	0.7589
46	0.3948 (log P)^2 + 2.4444 π^2_{Aro} - 0..0847 π^2_{Ali} - 1.4763 π_{Aro} + 0.2339 π_{Ali} + 1.7034	0.2070	0.8814
47	0.1602 (log P)^2 + 0.6433 σ_{Aro} - 0.0407 σ_{Ali} + 1.8251	0.2165	0.7156
48	0.1569 (log P)^2 + 0.6033 σ_{Aro} + 0.0059 σ_{Ali} - 0.7771 σ_I + 1.8017	0.2485	0.7197
49	0.2938 (log P)^2 + 0.3570 π^2_{Aro} - 0.0269 π^2_{Ali} + 1.0605 σ_{Aro} 0.2686 Es_{Ali} + 1.8744	0.2250	0.8581

(*Contd.*)

Table 5— Runs Showing Better Correlations (*S* and *R* values) of Set IV than Run 12b of Set I—*Contd.*

Run No	Governing equation (Y =)	*S*	*R*
50	0.3422 $(\log P)^2$ - 0.3992 π^2_{Aro} - 0.0273 π^2_{Ali} - 0.1161 Es_{Ali} + 1.8777	0.1909	0.8458
51	0.3737 $(\log P)^2$ + 0.3346 π^2_{Aro} - 0.0399 π^2_{Ali} + 1.1439 σ_{Aro} - 0.6014 σ_{Ali} + 3.7207 σ_I + 2.0102	0.2654	0.9037
52	0.2993 $(\log P)^2$ + 0.3288 π^2_{Aro} - 0.0272 π^2_{Ali} + 1.0287 σ_{Aro} - 0.2477 σ_{Ali} - 0.0104 Es_{Ali} + 1.8750	0.3182	0.8582
53	0.1769 log P + 0.2599 π^2_{Aro} - 0.0162 π^2_{Ali} + 1.1202 σ_{Aro} - 0.3251 σ_{Ali} + 1.3842 σ_I + 1.8973	0.4243	0.7290
54	0.1623 $(\log P)^2$ - 0.0365 log P + 0.4932 σ_{Aro} - 0.2214 σ_{Ali} + 0.0889 Es_{Ali} + 1.8243	0.3001	0.7289
55	0.1466 $(\log P)^2$ - 0.0279 log P + 0.4889 σ_{Aro} - 0.2827 σ_{Ali} + 0.2857 σ_I + 0.1072 Es_{Ali} + 1.8322	0.4243	0.7291
56	0.6733 $(\log P)^2$ - 0.3512 log P + 0.2749 σ_{Aro} - 0.1681 π_{Ali} + 0.9038 σ_{Aro} - 0.4409 σ_{Ali} + 2.0364	0.2267	0.9307
57	0.2336 $(\log P)^2$ - 0.0720 log P + 0.5382 σ_{Aro} + 0.0509 σ_{Ali} - 1.0116 σ_I + 1.7971	0.3014	0.7260
58	0.6870 $(\log P)^2$ - 0.2533 log P + 0.2504 π^2_{Aro} - 0.0819 π^2_{Ali} - 0.2472 π_{Aro} - 0.1893 π_{Ali} + 1.7595	0.2315	0.9276
59	0.6819 $(\log P)^2$ - 0.3050 log P - 0.0816 π^2_{Aro} - 0.0388 π^2_{Ali} + 0.0720 σ_{Aro} - 0.2380 σ_{Ali} + 1.9067	0.2264	0.9309
60	0.8218 $(\log P)^2$ - 0.3607 log P - 0.1901 π^2_{Aro} - 0.0446 π^2_{Ali} - 0.1212 Es_{Ali} + 1.9220	0.1383	0.9489
61	0.9556 $(\log P)^2$ - 0.4850 log P - 0.0676 π_{Aro} - 0.2142 π_{Ali} - 0.2407 Es_{Ali}	0.1201	0.9617

Table 6—Runs Showing Better Correlations (*S* and *R* values) of Set V than Run 12b of Set I

Run No	Governing equation (Y =)	*S*	*R*
62	-0.1828 log P + 0.6699 $(\log P)^2$ - 0.0754 $((\Sigma\pi)^2$ + 0.1967 $(\Sigma\pi)$ + 1.7235	0.0458	0.9409
63	0.2344 $(\log P)^2$ - 0.3666 $(\Sigma\sigma)$ - 0.1289 $(\Sigma\pi)$ + 1.9591	0.0762	0.7594
64	0.5005 $(\log P)^2$ - 0.0884 $(\Sigma\pi)^2$ + 0.2502 $(\Sigma\pi)$ + 1.6665	0.0508	0.9012
65	0.6693 $(\log P)^2$ - 0.3479 log P - 0.4405 $(\Sigma\sigma)$ - 0.1672 $(\Sigma\pi)$ + 2.0354	0.0495	0.9307

(*Contd.*)

Table 6— Runs Showing Better Correlations (*S* and *R* values) of Set V than Run 12b of Set I—*Contd*

Run No	Governing equation (Y =)	*S*	*R*
66	0.7446 $(\log P)^2$ - 0.3370 log P - 0.2004 (ΣEs) - 0.1602 $(\Sigma\pi)$ + 2.0383	0.0469	0.9381
67	0.3012 $(\log P)^2$ - 0.1355 $(\Sigma\pi)$ - 0.1269 $(\Sigma\sigma)$ - 0.1295 (ΣEs) + 1.9747	0.0842	0.7825
68	0.6753 $(\log P)^2$ - 0.1630 $(\Sigma\pi)^2$ + 0.6254 $(\Sigma\pi)$ + 0.5393 $(\Sigma\sigma)$ + 1.3550	0.0427	0.9489
69	0.7306 $(\log P)^2$ - 0.3560 log P - 0.1734 $(\Sigma\pi)$ - 0.2115 $(\Sigma\sigma)$ - 0.1235 (ΣEs) + 2.0499	0.0528	0.9479
70	0.6523 $(\log P)^2$ + 0.3040 log P + 1.2695 $(\Sigma\pi)$ - 0.2950 $(\Sigma\pi)^2$ + 1.3371 $(\Sigma\sigma)$ + 0.7993	0.0499	0.9536
71	0.7281 $(\log P)^2$ - 0.2522 log P - 0.0437 $(\Sigma\pi)^2$ + 0.0346 $(\Sigma\pi)$ - 0.1076 (ΣEs) + 1.8717	0.0488	0.9557
72	0.7698 $(\log P)^2$ - 0.1678 $(\Sigma\pi)^2$ + 0.6392 $(\Sigma\pi)$ + 0.8589 $(\Sigma\sigma)$ - 0.1584 (ΣEs) + 1.3565	0.0358	0.9764
73	0.7540 $(\log P)^2$ + 0.7632 (log P) - 0.5012 $(\Sigma\pi)^2$ - 2.2625 $(\Sigma\pi)$ + 3.0047 $(\Sigma\sigma)$ - 0.2290 (ΣEs) - 0.0381	0.0054	0.9997
74	0.3358 $(\log P)^2$ - 0.0316 $(\Sigma\pi)^2$ - 0.2544 $(\Sigma\sigma)$ + 1.8638	0.0658	0.8271
75	0.4118 $(\log P)^2$ - 0.0335 $(\Sigma\pi)^2$ - 0.1353 (ΣEs) + 1.8750	0.0611	0.8530
76	0.6700 $(\log P)^2$ - 0.2725 log P - 0.0346 $(\Sigma\pi)^2$ - 0.2369 $(\Sigma\sigma)$ + 1.8922	0.0477	0.9358
77	0.7345 $(\log P)^2$ - 0.2678 log P - 0.0362 $(\Sigma\pi)^2$ - 0.1257 (ΣEs) + 1.9021	0.0400	0.9552
78	0.4148 $(\log P)^2$ - 0.0333 $(\Sigma\pi)^2$ - 0.0198 $(\Sigma\sigma)$ - 0.1438 (ΣEs) + 1.8753	0.0706	0.8531
79	0.3629 $(\log P)^2$ - 0.0360 $(\Sigma\pi)^2$ - 0.3401 $(\Sigma\sigma)$ + 1.0083 σ_I + 1.8987	0.0750	0.8323
80	0.2308 $(\log P)^2$ - 0.1240 $(\Sigma\pi)$ - 0.3397 $(\Sigma\sigma)$ - 0.2562 σ_I + 1.9465	0.0879	0.7598
81	0.7367 $(\log P)^2$ - 0.2678 log P - 0.0361 $(\Sigma\pi)^2$ + 0.01460 $(\Sigma\sigma)$ - 0.1320 (ΣEs) + 1.9023	0.0490	0.9552
82	0.8759 $(\log P)^2$ - 0.3608 log P - 0.0512 $(\Sigma\pi)^2$ - 0.5408 $(\Sigma\sigma)$ + 3.6424 σ_I + 2.0275	0.0291	0.9845
83	0.4251 $(\log P)^2$ - 0.0355 $(\Sigma\pi)^2$ - 0.0408 $(\Sigma\sigma)$ - 0.1363 (ΣEs) + 0.5396 σ_I + 1.8934	0.0861	0.8545
84	0.2964 $(\log P)^2$ - 0.1224 $(\Sigma\pi)$ - 0.0301 $(\Sigma\sigma)$ - 0.1404 (ΣEs) - 0.7272 σ_I + 1.9402	0.1025	0.7855
85	0.8002 $(\log P)^2$ - 0.1949 $(\Sigma\pi)^2$ + 0.7224 $(\Sigma\pi)$ + 0.4336 $(\Sigma\sigma)$ + 2.6913 σ_I + 1.3692	0.0343	0.9783

(*Contd.*)

Table 6— Runs Showing Better Correlations (S and R values) of Set V than Run 12b of Set I—*Contd.*

Run No	Governing equation (Y =)	S	R
86	$0.8967 (\log P)^2 - 0.3487 \log P - 0.0505 (\Sigma\pi)^2 - 0.3517 (\Sigma\sigma) - 0.0829 (\Sigma Es) + 3.2694 \sigma_I + 2.0200$	0.0308	0.9913
87	$0.9112 (\log P)^2 - 0.4724 \log P - 0.2526 (\Sigma\pi) - 0.7246 (\Sigma\sigma) - 0.0666 (\Sigma Es) + 3.6227 \sigma_I + + 2.2491$	0.0337	0.9896
88	$0.9081 (\log P)^2 - 0.5511 \log P + 0.0274 (\Sigma\pi)^2 - 0.3940 (\Sigma\pi) - 1.0687 (\Sigma\sigma) + 4.1144 \sigma_I + 2.3842$	0.0400	0.9853
89	$4.3139 \log P + 13.3998 (\Sigma\sigma) - 1.8591 (\Sigma\pi)^2 + 9.1545 (\Sigma\pi) - 0.6507 (\Sigma Es) - 12.1358 \sigma_I - 6.4051$	0.0963	0.9116
90	$0.8560 (\log P)^2 - 0.1934 (\Sigma\pi)^2 + 0.7172 (\Sigma\pi) + 0.7119 (\Sigma\sigma) - 0.1290 (\Sigma Es) + 2.2354 \sigma_I + 1.3680$	0.0227	0.9953

Table 7— Predicted log of Antineoplastic Activity of Best Correlation Obtained in Sets I-V of 5-N-Substituted-2-*p*-substituted Benzenesulphonyl-L-Glutamines (I)

Compd	Predicted log of % inhibition of tumor wt				
	Set I (Run 12b)	Set II (Run 14)	Set III (Run 35)	Set IV (Run 61)	Set V (Run 73)
1a	1.8596	1.9152	1.8422	1.8410	1.8428
2a	1.8453	1.8965	1.8418	1.8594	1.8489
3a	1.8344	1.8499	1.8932	1.9147	1.9056
4a	1.8313	1.7940	1.7825	1.7665	1.7819
1b	1.7196	1.7091	1.8449	1.7843	1.8257
2b	1.7575	1.6981	1.6890	1.7228	1.6831
3b	1.8645	1.7865	1.8776	1.8756	1.8755
4b	1.7128	1.7274	1.6537	1.6606	1.6614

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Notes

A New Route to 19-Norsteroids

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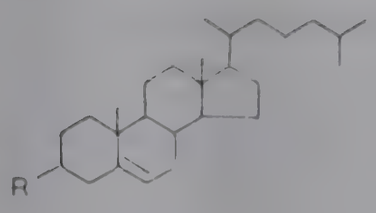
Cholesterol has been successfully converted into 19-norcholesta-1(10), 5-dienyl-3β-acetate(II) via 19-hydroxycholest-5-enyl-3β-acetate(IV).

Owing to the medicinal importance of 19-norsteroids and other estrone derivatives as contraceptives and hormonal drugs, extensive work has been done[1,2] for the preparation of these derivatives from cheaply available sterols. In the present note we report a procedure for the conversion of cholesterol(I) into 19-norcholesta-1(10), 5-dienyl-3β-acetate(II).

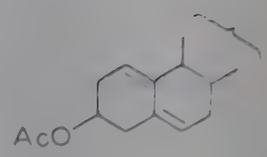
The melting point reported is uncorrected. Homogeneity of compounds was checked by TLC and silica gel. Petrol used had the boiling point 60-80°. PMR spectrum was recorded on a Varian XL-200 (200 MHz) instrument using TMS as internal standard.

19-Norcholesta-1(10), 5-dienyl-3β-acetate(II)

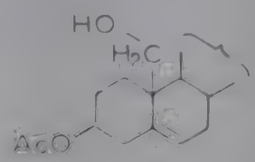
19-Hydroxycholest-5-enyl-3β-acetate(IV, 100 mg), prepared from cholesteryl acetate(III) by reported procedures[3-7], was taken in a suspension of lead tetraacetate (500 mg, freshly crystallised from acetic acid and dried over KOH under reduced pressure) and cupric acetate (500 mg) in dry toluene (30 ml). The mixture was refluxed under N_2 for 8 hr, filtered after cooling rapidly in ice and the greenish coloured filtrate washed with 6*N* HCl (4 × 100 ml) to remove the excess cupric acetate. Toluene was removed by steam distillation and the product taken up in ether. Usual work-up furnished a gummy residue (120 mg) which was chromatographed over a column of silica gel (10 g, 60-100 mesh). Petrol-benzene (7:3) eluates on crystallisation from chloroform-methanol yielded colourless needles of II (45 mg), m.p. 67-68° (Found: C, 81.3; H, 10.9; M^+ 412. $C_{28}H_{44}O_2$ requires C, 81.5; H, 10.8%; M^+ 412); UV(EtOH): 240-245 nm (ε 37080, heteroannular diene); IR(KBr): 1740, 1235 (acetate); 840 cm^{-1} (trisubstituted double bond); PMR($CDCl_3$): δ 5.50 (olefinic proton at C-1, *m*, 1H), 5.38 (olefinic proton at C-6, *m*, 1H), 5.0 (C_3-αH, *m*, 1H), 2.02 (acetoxy methyl, *s*, 3H); MS: *m/z* 412 (M^+), 368, 350 (base peak, M-60), 337, 169, 156, 130. The mass spectral data were in excellent agreement with those reported by Djerassi *et al.*[8] for compounds of similar structures.



I, R = OH
III, R = OAc



II



IV

When the reaction was carried out in dry benzene and also in *m*-xylene under identical conditions, the yield of II was considerably less (15% and 25% respectively).

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Synthesis of 14-Methylpentadecan-3-one

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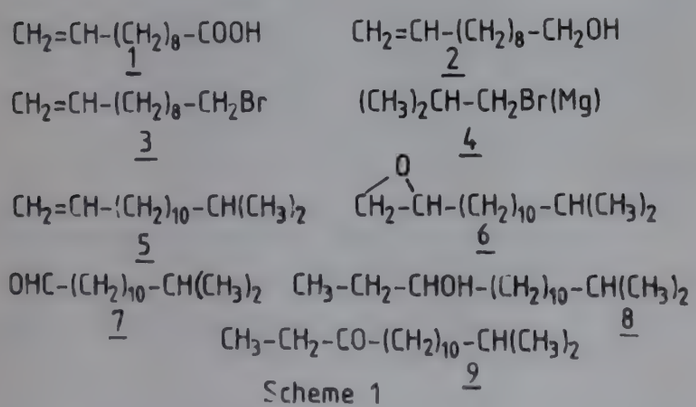
An unambiguous synthesis of the title compound (**9**), isolated recently by Haque *et al.* [*J Indian chem Soc*, **61** (1984) 92] from the pet. ether extract of *Parthenium hysterophorous* Linn. is described. Significantly the natural compound has been isolated as a solid (m.p. 80°) while our synthetic product is an oil (b.p. 118-20°/0.4 mm). Besides this some of the reported spectral data do not tally with those of synthetic **9**.

Recently Haque *et al.*[1] have isolated a granular white solid compound, m.p. 80°, from petroleum ether extract of *Parthenium hysterophorous* Linn. (Compositeae) and proposed its structure as 14-methylpentadecan-3-one (**9**), on the basis of spectroscopic data. We report herein an unequivocal synthesis of **9** (Scheme 1). Further we wish to record that while synthetic **9** is an oil, the Haque *et al.*[1] have obtained it as a solid (m.p. 80°). Some of the spectral data of synthetic **9** are not in accord with those reported by Haque *et al.*[1].



Scheme 1

Undecenoic acid was converted into undecenyl alcohol (**2**) which on bromination[2] with PPh_3Br_2 in methylene chloride gave the bromide (**3**) in almost quantitative yield. **3** was coupled with the Grignard reagent prepared from 1-bromo-2-methylpropane (**4**)[3] in tetrahydrofuran (THF) at −10°C in the presence of catalytic amount (0.3 %) of Li_2CuCl_4 (ref. 4) to give the olefin (**5**) which on epoxidation with *m*-CPBA in methylene chloride followed by oxidative cleavage of the epoxide (**6**) with HIO_4 in THF gave the aldehyde (**7**). Ethylmagnesium bromide was allowed to react with **7** and the product (**8**) thus obtained on PCC[5] oxidation in methylene chloride afforded the desired product (**9**) as an oil.

Compound (**9**) displayed characteristic IR bands at 1720 ($\geq C=O$), 1385 and 1375 cm^{-1} (isopropyl) and PMR signals at δ 0.85 [*d*, 6H, $-CH(CH_3)_2$], 1.02 (*t*, 3H, $-CH_2-CH_3$) and 2.2-2.6 (*m*, 4H, CH_2-COCH_2-CH_3). Its MS showed M^+ ion at *m/z* 240 and the other prominent fragments at *m/z* 221, 85, 57 (base peak) and 43. These data are consistent with structure (**9**). However, Haque *et al.*[1] isolated **9** as a solid (m.p. 80°) and reported IR bands at 1750 (carbonyl), 1481 and 1471 (isopropyl) for the natural product. These discrepancies cast doubt on the purity of the isolated product. We failed in our attempts to get an authentic sample of natural **9**.

IR spectra (ν_{max} in cm^{-1}) were recorded as thin films on a Perkin-Elmer infracord 137-B spectrophotometer, PMR spectra (chemical shift in δ-scale) in $CDCl_3$ on a Varian A 60-A spectrometer using TMS as an internal standard and the mass spectra on a VG Micromass 7070 F instrument. TLC was done on silica gel plates with benzene as solvent, unless otherwise stated.

Anhydrous solvents were prepared by distillation over lithium aluminium hydride (ether, THF) with prior drying over phosphorus pentoxide (ether) and potassium hydroxide pellets (THF) respectively.

Undecenyl bromide (**3**)

To a stirred and cooled (0-5°C) suspension of triphenylphosphine (19.36 g, 0.074 mol) in anhydrous methylene chloride (100 ml), bromine in CCl_4 (13.24 ml of 5.5 molar Br_2 in CCl_4) was added dropwise during 10 min. After stirring for a further 10 min, the cooling bath was removed and the system flushed with nitrogen to remove the excess of bromine vapours. To the resulting thick white suspension of Ph_3PBr_2, a solution of undecenyl alcohol (**3**, 9 g, 0.053 mol) and anhydrous pyridine (6.35 ml) in methylene chloride (33 ml) were added dropwise during 30 min. The stirring was continued for 2 hr, the solvent was carefully removed over a rotatory evaporator and the residue repeatedly washed with pet. ether (60-80°). The combined organic extract was filtered, the solvent removed, the residue dissolved in pet. ether and passed through a short (2 inch) pad of alumina. Removal of solvent afforded the bromide (**3**) in quantitative yield (12.1 g, 98.06%); b.p. 115°/5 mm (lit.[6] b.p. 136-38°/15 mm); n_D^{23} 1.4638; IR: 3105, 2975, 2875, 1655, 1470, 1000 and 915; PMR: 1.32 (*bs*, 14H, 7 × $-CH_2-$), 2.0 (*bm*, 2H, $-CH_2-CH=CH_2$), 3.4 (*t*, 2H, J=6Hz, $-CH_2Br$), 4.85-6.20 (*m*, 3H, $-CH=CH_2$).

13-*Methyltetradec*-1-*ene* (**5**)

The Grignard reagent was prepared from Mg turnings (1.08 g), 1-bromo-2-methylpropane[3] (**4**) (4.11 g, 0.03 mol) in THF. To this reagent were added, catalytic quantity of Li_2CuCl_4 (6.7 ml of 0.3% in THF) followed by undecenyl bromide (**3**) (6.99 g, 0.03 mol) in anhydrous THF (20 ml) during 30 min. The temperature of the reaction mixture was maintained between $-10°$ to $-20°C$ for 3 hr, gradually brought to room temperature and left overnight under stirring. The reaction was quenched by adding saturated aq. ammonium chloride (2-3 ml) and stirred. Distilled pet. ether (60-80°, 60 ml) was then added. The flask was thoroughly washed and then the combined petroleum ether extract passed through a pad of silica gel (column chromatography grade). Removal of solvent followed by distillation yielded **5** (5.7 g), b.p. 118°/5 mm; IR: 3100, 2975, 2875, 1650, 1465, 1390, 1370, 990, 900 and 720; PMR: 0.85 [*d*, 6H, $J=6Hz$, $-CH(CH_3)_2$], 1.28 (*bs*, 18H, $9\times -CH_2-$), 2.10 [(*bm*, 3H, $-CH_2-CH=CH_2$ and $-CH(CH_3)_2$], 4.80-6.25 (*m*, 3H, $-CH=CH_2$ (Found: C, 85.6; H, 14.3. $C_{15}H_{30}$ requires C, 85.7; H, 14.3%).

1,2-*Epoxy*-13-*methyltetradecane* (**6**)

To a solution of **5** (3.15 g, 0.075 ml) in anhydrous methylene chloride (30 ml) *m*-CPBA (60%, 12 g) was added at 0°C in portions. It was stirred for 2 hr and kept overnight in the refrigerator. The solid material was diltered off and the organic layer successively washed with saturated aq. $NaHSO_3$, 5% aq. Na_2CO_3, water and brine. The resulting solution being cloudy was passed through a short column of neutral alumina and dried (Na_2SO_4). Removal of the solvent gave **6** as an oil in almost quantitative yield and was used as such in the next step; IR: 2975, 2865, 1465, 1385, 1375, 1205, 1075, 1035, 705 and 680; PMR: 0.88 [*d*, 6H, $J=6Hz$, $-CH(CH_3)_2$], 1.28 (*bs*, 18H, $9\times -CH_2-$), 2.25-2.90 [*m*, 4H, – oxirane CH and CH_2 and $CH(CH_3)_2$]; TLC: single spot, iodine active, R_f 0.7.

12-*Methyltridecan*-1-*al* (**7**)

To an ice-cooled and stirred solution of $HIO_4.2H_2O$ (4.84 g of 50% w/w solution, 0.010 mol) in THF (20 ml) was added a solution of **6** (2.26 g, 0.010 mol) in ether (50 ml), stirred for 4 hr and then poured into ice-cold water. This was extracted with ether and the organic extract successively washed with aq. $NaHSO_3$, aq. $NaHCO_3$, water and brine and dried (Na_2SO_4). Removal of solvent yielded **7** as an oil (1.40 g, 66.04%); IR (film): 2975, 2875, 2725, 1730, 1465, 1385 and 1375; PMR: 0.88 [(*d*, 6H, $J=6Hz$, $-CH(CH_3)_2$], 1.30 (*bs*, 18H, $9\times -CH_2-$), 2.30-2.43 (*m*, 2H, CH_2-CHO), 9.86 (*t*, 1H, $J=1.5Hz$, $-CHO$); TLC: single spot, DNPH positive, R_f 0.6.

14-*Methylpentadecan*-3-*ol* (**8**)

To Grignard reagent prepared from Mg (0.18 g, 1.3 equiv), ethyl bromide (0.66 g, 0.006 mol) in ether (10 ml) was added a solution of **7** (1.06 g, 0.005 mol) in ether (10 ml) dropwise at 0° to $-10°$. The reaction mixture was stirred further and slowly brought to room temperature during 4 hr and left overnight. The reaction was quenched by the addition of saturated aq. ammonium chloride (3 ml), stirred, extracted with ether, and the organic extract successively washed with aq. $NaHCO_3$ (5%), water and brine and dried (Na_2SO_4). Removal of solvent yielded **8** (0.90 g) as an oil. The analytical sample was prepared by PTLC; IR: 3400, 2975, 2875, 1470, 1380 and 1370; PMR: 0.87 [*d*, 6H, $J=6Hz$, $-CH(CH_3)_2$], 0.93 (*t*, one of it overlapped on doublet of isopropyl, 3H, $J=7Hz$, $-CH_2CH_3$), 1.30 (*bs*, 14H, $7\times -CH_2-$), 1.48 (*s*, 4H, $-CH_2-CHOH-CH_2$), 3.60-3.70 (*m*, 1H, $-CHOH$); TLC: single spot, iodine active, R_f 0.4 (Found: C, 79.1; H, 13.9. $C_{16}H_{34}O$ requires C, 79.3; H, 14.0%).

14-*Methylpentadecan*-3-*one* (**9**)

To dry pyridinium chlorochromate (PCC) (0.864 g, 0.004 mol) in anhydrous methylene chloride (20 ml) was added **8** (0.726 g, 0.003 mol) in anhydrous methylene chloride (15 ml) in one lot while stirring. In a short time a black mass separated. The stirring was continued for further 3 hr. To this mixture, anhydrous ether (20 ml) was added and the supernatant decanted from the solid residue. The residue was washed with anhydrous ether (2×20 ml), and the combined ether extract passed through a small bed of florosil (10 g). Removal of the solvent afforded **9** in good yield (0.6 g, 83.33%); b.p. 118-20°/0.4 mm. IR: 2965, 2860, 1720, 1460, 1385 and 1375 PMR: 0.85 [*d*, 6H, $J=6Hz$, $-CH(CH_3)_2$], 1.02 (*t*, two of the triplets overlap with one of the doublets of isopropyl, 3H, $J=7.5Hz$, $-CH_2CH_3$), 1.6-2.0 [*m*, 1H, $(CH_3)_2$], 2.2-2.6 (*m*, 4H, $-CH_2-CO-CH_2CH_3$); n_D^{26} 1.4436; MS: *m/z* 240 (M^+), 221 (M-29), 197 (M-43) 85, 57 (base peak) and 43; TLC: single spot, iodine active and DNPH positive, R_f 0.7 (Found: C, 79.8; H, 13.0. Calc. for $C_{16}H_{32}O$: C, 80.0; H, 13.3%).

One of the authors (SVT) is thankful to the Department of Atomic Energy, for the award of a research fellowship.

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A New Synthesis of *ar*-Todomatuic Acid & Its Methyl Ester (*ar*-Juvabione)

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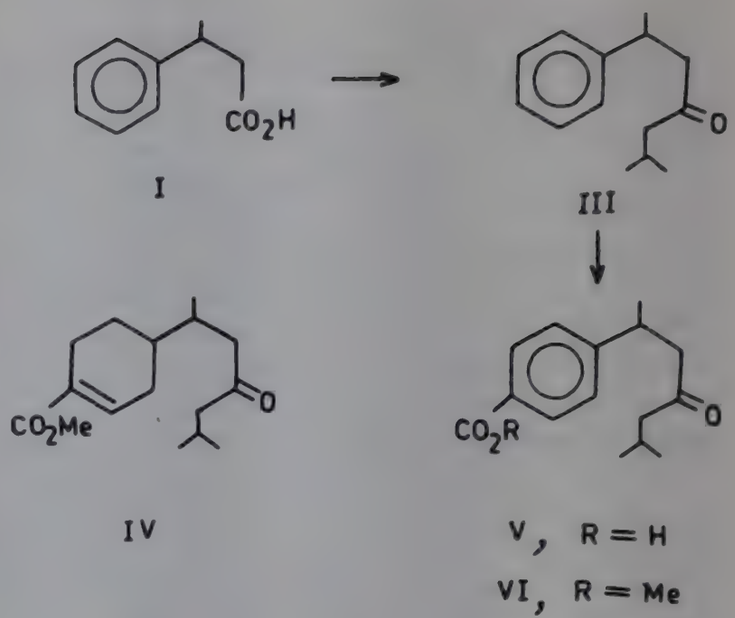
Reaction of isobutyllithium with 3-phenylbutyric acid results in the formation of 2-phenyl-6-methylheptan-4-one(III), which on reaction with oxalyl chloride under Friedel-Crafts condition furnishes *ar*-todomatuic acid (V). Work-up of the above reaction with dry methanol instead of water gives *ar*-juvabione (VI).



I III IV V, R = H VI, R = Me

Sakai and Hirose[1] reported the isolation of *ar*-todomatuic acid (V) from the Douglas fir. The methyl ester of *ar*-todomatuic acid known as *ar*-juvabione (VI) exhibited juvenile hormone activity similar to that of natural juvabione (IV). Mane and Krishna Rao[2] as well as Ayyar and Krishna Rao[3] have reported the synthesis of VI. The present synthesis was undertaken with a view to finding a short and efficient route for VI.

Friedel-Crafts alkylation of benzene with crotonic acid gave 3-phenylbutyric acid[4] (I) which on reaction with isobutyllithium in dry ether gave 2-phenyl-6-methylheptan-4-one (III). The ketone (III) was also prepared from styryl isobutyl ketone (II) by conjugate addition of methylmagnesium iodide in the presence of cuprous chloride[3]. The ketone (III) was condensed with oxalyl chloride[5] using anhydrous aluminium chloride to furnish *ar*-todomatuic acid (V), identical in all respects with the reported one[2]. V on esterification furnished VI. Compound(VI) could also be directly prepared from III by reaction with oxalyl chloride followed by work-up with dry methanol.

2-Phenyl-6-methylheptan-4-one (III)

Isobutyllithium [prepared from isobutylbromide (42 g) and lithium (4.5 g) in dry ether (225 ml)] was added to a solution of 3-phenylbutyric acid (27 g) in dry ether (120 ml) at 0° with stirring. The reaction mixture was stirred at room temperature for 6 hr and decomposed by pouring into ice-water (250 ml). The organic layer was separated and the aqueous layer extracted with ether. The combined ether extract was washed with water and dried. Removal of solvent followed by distillation under reduced pressure furnished III (10 g), b.p. 125-26°/15 mm; IR (neat): 1718, 1610 cm^{-1}, PMR (CCl_4): δ 0.82 [6H, *d*, $J=7$ Hz, $CH(CH_3)_2$], 1.23 (3H, *d*, $J=7$ Hz, $-CH_3$), 2.05 (3H, *m*, $-CH_2-$ and CH), 2.55 (2H, *m*, $-CH_2-$), 3.25 (1H, sextet, $J=7$ Hz, Ph$-\overset{|}{C}-$H), 7.05 (5H, *m*, Ar-H) (Found: C, 82.1; H, 9.7. $C_{14}H_{20}O$ requires C, 82.4; H, 9.8%).

ar-Todomatuic acid (V)

To a stirred mixture of anhydrous aluminium chloride (7 g) and oxalyl chloride (5 ml) in dry carbon disulphide (30 ml) was added III (2 g in 10 ml CS_2) at 0° during 30 min. The reaction mixture was stirred at 0° for 2 hr and at room temperature for 1 hr; poured into ice-water, the organic layer separated and the aqueous layer extracted with ether. The combined organic layer was washed with water, extracted with saturated aq. sodium carbonate, the carbonate layer acidified to yield an oily product which was extracted with ether. The ether layer was washed with water, and dried. Removal of solvent furnished V which solidified on the addition of a little pet. ether. It was recrystallized from pet. ether, m.p. 80-81° (lit.[2] 77-78°) (1.2 g), identical (m.p., IR, UV and PMR) with an authentic sample[2].

ar-Juvabione (VI)

Ketone (III) was reacted with oxalyl chloride as described in the above experiment. The reaction mixture was treated with dry methanol under cooling instead of addition to water. After stirring with methanol for 30 min the reaction mixture was poured into water, the organic layer separated and the aqueous layer extracted with ether. Combined organic layer was washed with aq. sodium carbonate, water and dried. Removal of solvent furnished VI which was purified by chromatography over silica gel. It was identical (IR, UV and PMR) with a sample prepared by the esterification of *ar*-todomatuic acid (V).

We thank the CSIR, New Delhi and the Department of Atomic Energy, Bombay for financial assistance.

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Synthesis of Methyl 5α-Hydroxy-2-oxo-eudesm-3-en-13-oate

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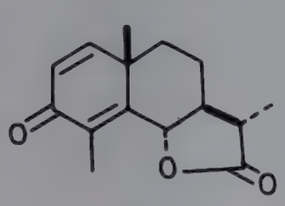
A new route for the preparation of 3-oxo-eudesm-4-en-13-oic acid (**2**) from (−)-1-santonin (**1**) and its transformation to the title compound (**10**) have been described. The Δ^4-3-keto acid (**2**) is prepared by catalytic hydrogenation of **1** to dihydrosantonin (**4**) followed by epimerisation at C_6-centre and reduction of 6-*epi*-dihydrosantonin (**5**) with zinc/acetic acid. The methyl ester (**3**) of this acid (**2**) is reduced with sodium borohydride to a mixture of allylic alcohols and subsequently dehydrated to the diene (**7**). Photooxygenation of **7** with eosin as sensitizer gives the endoperoxide (**8**), which rearranges to the title compound (**10**) on basic alumina.

During our study on transformation of (−)-1-santonin (**1**) to various natural products and potential eudesmanoic intermediates, it was felt necessary to prepare Δ^4-3-keto acid (**2**) in substantial amounts by a convenient route. Preparation of **2** has been reported earlier by Rao *et al.*[1] using Birch reduction. However, an alternate method using simple reagents and less stringent conditions could also yield the desired acid (**2**).

The new preparative route was developed on parallel lines to that reported by Piers *et al.*[2] Santonin (**1**) was hydrogenated using Raney nickel in a Parr hydrogenator to dihydrosantonin (**4**), m.p. 99-100° (lit.[2], 101-2°). Epimerisation of **4** at C_6-centre was brought about in the presence of DMF and HCl, at 80° to furnish 6-epidihydrosantonin (**5**), m.p. 121-22°. It analysed for $C_{15}H_{20}O_3$; M^+ 248; UV (EtOH): 253 nm (ε, 14,400); IR: 1780 (lactone carbonyl), 1680 (conjugated ketone) and 1620 cm^{-1} (double bond); PMR: δ 5.5 (1H, doublet, $J = 6$ Hz, C_6-H).

A methanolic solution of **5** when treated with activated zinc powder and acetic acid at 60°, furnished Δ^4-3-keto acid (**2**) in a quantitative yield, m.p. 122-23° (lit.[1], m.p. 123-24°). It was characterized by m.m.p., superimposable spectra and preparation of derivatives.

The methyl ester (**3**) of **2** was reduced with sodium borohydride in ethanol at room temperature to furnish a mixture of allylic alcohols (**6**), which was found to be highly unstable. It furnished **7** when treated with



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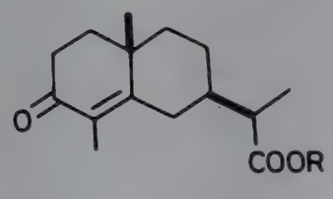
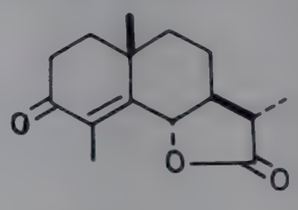


(2) R = H
(3) R = CH_3



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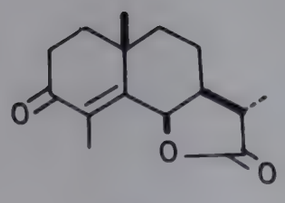

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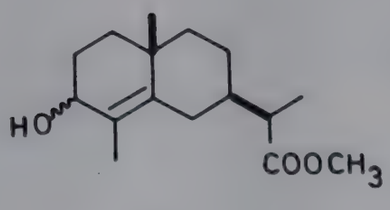

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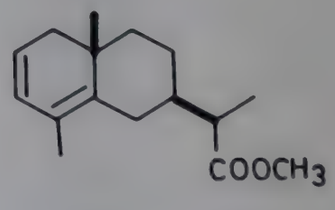

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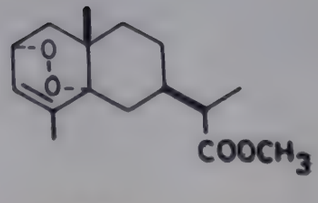

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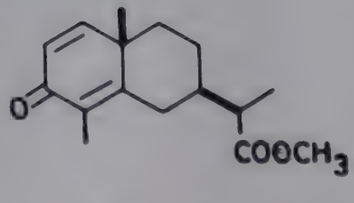

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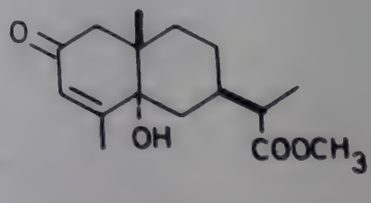

(10)

Woelm grade-I alumina impregnated with 2% pyridine at 230-235°, in a rapid current of dry nitrogen. However, a solution of **7** in benzene at room temperature was relatively stable. It analysed for $C_{16}H_{24}O_2$; M^+ 248; UV (EtOH): 269 nm (ε, 6400); IR: 1730 (ester carbonyl) and 1615 cm^{-1} (double bond). Its PMR spectrum displayed a characteristic doublet at δ 1.72 (J= 1Hz) for the C_4-methyl protons and a multiplet at 5.68 for the C_2-H and C_3-H protons, as observed for similar 2,4-*cis*-diene systems[3,4].

The photooxygenation of the diene (**7**) in ethanol-benzene (1:1) using eosin as sensitizer, with tungsten halogen lamp (24 V, 150 W), gave endoperoxide (**8**) and the keto ester **9** which were separated by column chromatography over silica gel.

Compound **8** analysed for $C_{16}H_{24}O_4$, M^+ 280, IR: 1730 (ester carbonyl) and 1650 cm^{-1} (double bond). Its PMR spectrum displayed a doublet (J=1.5 Hz) at δ 1.8 due to C_4-methyl protons, a singlet at 3.8 for the ester methyl protons and multiplets centered at 4.48 and 6.2 for C_2-H and C_3-H protons respectively, apart from the other methyl proton signals.

Compound **9** analysed for $C_{16}H_{22}O_3$, M^+ 262, UV (EtOH): 245 nm (ε, 14,150), IR: 1730 (ester carbonyl), 1660 (unsaturated ketone) and 1615 cm^{-1} (double bond); PMR spectrum exhibited a singlet at δ 1.95 for the C_4-methyl protons, doublets (J=10 Hz) centered at 6.21 and 6.81 due to C_2-H and C_1-H protons respectively, alongwith the regular signal pattern for the expected endesmane skeleton. Based on these evidences, the structure assigned to this compound was methyl 3-oxo-eudesma-1,4-dien-13-oate (**9**).

The endoperoxide (**8**) when left in contact with basic alumina (E Merck, grade-I) for 18 hr gave **10** in a good yield. Use of alkali was avoided due to fear of the ester hydrolysis and possible epimeric changes. This compound (**10**) analysed for $C_{16}H_{24}O_4$, M^+ 280, UV (EtOH): 240 nm (ε, 12,160), IR: 3540 (hydroxyl) and 1680 cm^{-1} (conjugated ketone). Its PMR spectrum displayed signals at δ 1.7 as a singlet (D_2O exchangeable) due to C_5-hydroxyl proton, 1.96 as a doublet (J=1 Hz) for the C_4-methyl protons and a broad singlet at 5.81 for C_3-H proton.

The spectral evidences agreed well with the assigned structure (**10**) and its main spectral characteristics were comparable with similar ring-A modified compounds cited in literature[3,4].

All melting points are uncorrected. UV spectra were recorded on a Perkin Elmer model 137, UV-visible spectrophotometer and varian superscan-3. The IR spectra were recorded on a Perkin Elmer 237-B grating spectrophotometer (ν_{max} in cm^{-1}). PMR spectra were recorded in $CDCl_3$ on a Varian 100 MHz instrument with TMS as internal standard (chemical shifts in δ, ppm). Anhydrous Na_2SO_4, was used for drying the organic extracts.

Hydrogenation of Santonin (**1**)

Hydrogenation of **1** was carried out according to the procedure reported by Piers *et al.*[2], m.p. 99-100° (lit.[2], m.p. 101-2°).

Epimerisation of **4**

Dihydrosantonin (**4**, 5 g) was dissolved in DMF (100 ml) containing 5% HCl. The resulting solution was heated to 85-90° for 3.5 hr, allowed to stand overnight, diluted with water and extracted thoroughly with $CHCl_3$. The combined extracts were washed with saturated $NaHCO_3$ solution followed by water, brine and dried. Removal of solvent furnished the crude product (4.8 g) which was purified by chromatography over silica gel (60 g) to give pure **5** (4 g) m.p. 121-22°, IR: 1780 (lactone $\succ C=O$), 1680 (ketone $\succ C=O$), 1620 ($\succ C=C\prec$); PMR: 1.28 (3H, *s*, C_{10}-CH_3), 1.38 (3H, *d*, J=8 Hz, C_{11}-CH_3), 1.94 (3H, *s*, C_4-CH_3), and 5.5 (1H, *d*, J=6 Hz, C_6-H) (Found: C, 72.1; H, 8.2. $C_{15}H_{20}O_3$ requires C, 72.6, H, 8.1%).

Zinc/AcOH reduction of **5**

To a solution of **5** (4 g) in methanol (100 ml) were added AcOH (5 ml) and zinc dust (4 g). The resulting mixture was refluxed gently for 15 min. under N_2 atmosphere. At the end, the reaction mixture was cooled, filtered and the filtrate concentrated. Addition of ether precipitated the inorganic impurities which were filtered off. The etheral layer was washed with saturated $NaHCO_3$ solution to remove the acidic materials. The aqueous bicarbonate layer was acidified with 2N HCl and the liberated crude acid **2** (3.6 g) crystallised from ethyl acetate-pet. ether, m.p. 122-23° (lit.[1], m.p. 123-24°), m.m.p. 122-23°.

Its methyl ester (**3**) gave 2,4-DNP derivative, m.p. 164-65° (lit.[1], m.p. 164-66°), and semicarbazone derivative, m.p. 210-12° (d) [lit.[1], m.p. 211-12° (d)].

Sodium borohydride reduction of **3**

$NaBH_4$ (0.38 g) dissolved in abs. ethanol (10 ml) was gradually added to a stirred and pre-cooled (0°) solution of **3** (2.6 g) in abs. ethanol (55 ml). It was stirred for 1.5 hr and allowed to stand overnight. Work-up involved removal of ethanol *in vacuo* and extraction with ether. Removal of ether afforded the unstable methyl 3-hydroxyeudesm-4-en-13-oate (**6**, 2.4 g) IR: 3510 (−OH), 1730 ($-COOCH_3$), 1620 ($\succ C=C\prec$) (Found: C, 72.1, H, 9.7. $C_{16}H_{26}O_3$ requires C, 72.2, H, 9.8%).

Dehydration of **6**

The mixture of allylic alcohols (**6**, 2 g) was throughly mixed with 2% pyridine impregnated alumina (3 g,

Woelm, neutral grade-I). The reaction mixture was heated in an air bath at 230-40° for 2.5 hr in a rapid current of nitrogen. After cooling, the crude reaction product was extracted with chloroform. The $CHCl_3$ layer was washed with 10% HCl, water and brine.

Removal of $CHCl_3$ afforded a mixture of two products which was chromatographed over silica gel (35 g).

Fraction (*i*): The least polar compound was eluted with 3% ethyl acetate-pet. ether was identified as methyl eudesm-2,4-dien-13-oate (**7**, 0.48 g), UV (EtOH): 269 nm (ε, 6400), IR: 1730 ($-COOCH_3$), 1620 ($>C=C<$), 1590 ($>C=C<$); PMR: 0.88 (3H, *d*, $J=6$ Hz, C_{11}-CH_3), 0.99 (3H, *s*, C_{10}-CH_3), 1.72 (3H, *d*, $J=1$ Hz, C_4-CH_3), 3.76 (3H, *s*, $-COOCH_3$) and 5.68 (2H, br, *s*, C_2- and C_3-H) (Found: C, 77.0, H, 9.4. $C_{16}H_{24}O_2$ requires C, 77.4, H, 9.7%).

Fraction (*ii*): Eluted with 5% ethyl acetate-pet. ether to furnish methyl 3-oxo-4β H, 5αH-eudesman-13-oate, identified by direct comparison with the one reported in literature[1].

Photooxygenation of the diene **7**

A solution of **7** (0.5 g) and eosin (10 mg) dissolved in ethanol-benzene (1:1, 50 ml) was taken in a photochemical reactor provided with a condenser, guard tube and gas inlet. The solution was irradiated by a tungsten halogen lamp (24 V, 150 W), while a steady current of oxygen was bubbled through it. After 20 hr, the solvent was removed under reduced pressure, the crude product diluted with water and extracted with benzene. The benzene layer was washed with water, brine and dried. Evaporation of the solvent gave a mixture of two products (0.51 g) besides a small amount of the starting material. Consequently, it was chromatographed over silica gel and followed fractions were collected.

Fraction (*i*): Eluates from 2% ethyl acetate-pet. ether furnished the unreacted diene (**7**, 0.08 g).

Fraction (*ii*): Elution with 4.5% ethyl acetate-pet. ether afforded a solid (0.141 g) which crystallised from the same solvent system, m.p. 60-61° and characterised as the endoperoxide **8**; IR: 1730 ($-COOCH_3$), 1650 ($>C=C<$); PMR: 0.94 (3H, *s*, C_{10}-CH_3), 1.2 (3H, *d*, $J=6$ Hz, C_{11}-CH_3), 1.8 (3H, *d*, $J=1.5$ Hz, C_4-CH_3), 3.8 (3H, *s*, $-COOCH_3$), 4.48 (1H, *m*, C_2-H) and 6.2 (1H, *m*, C_3-H) (Found: C, 68.4, H, 8.6. $C_{16}H_{24}O_4$ requires C, 68.6, H, 8.6%).

Fraction (*iii*): Elution with 5.5% ethyl acetate-pet. ether furnished methyl 3-oxo-eudesma-1,4-dien-13-oate (**9**, 0.095 g), UV (EtOH): 245 nm (ε, 14,150), IR: 1730 ($-COOCH_3$), 1660 ($>C=O$), 1610 ($>C=C<$); PMR: 1.24 (3H, *s*, C_{10}-CH_3), 1.26 (3H, *d*, $J=6$ Hz, C_{11}-CH_3), 1.92 (3H, *s*, C_4-CH_3), 3.78 (3H, *s*, $-COOCH_3$), 6.24 (1H, *d*, $J=10$ Hz, C_2-H) and 6.76 (1H, *d*, $J=10$ Hz, C_1-H).

Rearrangement of **9** *to* **10**

The endoperoxide **9** (0.1 g) was thoroughly mixed with alumina (0.5 g, E Merck grade, basic activity-I). The mixture was then placed on a column saturated with ether and stored at ambient temperature for 18 hr to complete the rearrangement. The light yellow alumina was placed in a porous thimble of soxlet extractor and the rearranged product extracted with ether. Evaporation of ether gave **10**, UV (EtOH): 240 nm (ε, 12,160), IR: 3450 ($-OH$), 1730 ($-COOCH_3$), 1680 ($>C=O$), 1625 ($>C=C<$); PMR: 1.0 (3H, *s*, C_{10}-CH_3), 1.18 (3H, *d*, $J=6$ Hz, C_{11}-CH_3), 1.7 (1H, *s*, D_2O exchangable, C_5-OH), 1.96 (3H, *d*, $J=1$ Hz, C_4-CH_3), 3.72 (3H, *s*, $-COOCH_3$) and 5.8 (1H, br, *s*, C_3-H) (Found: C, 68.3, H, 8.6. $C_{16}H_{24}O_4$ requires C, 68.6, H, 8.6%).

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Ring Reduction Studies of Hydrocarbons Using Cs-K-Na Alloy

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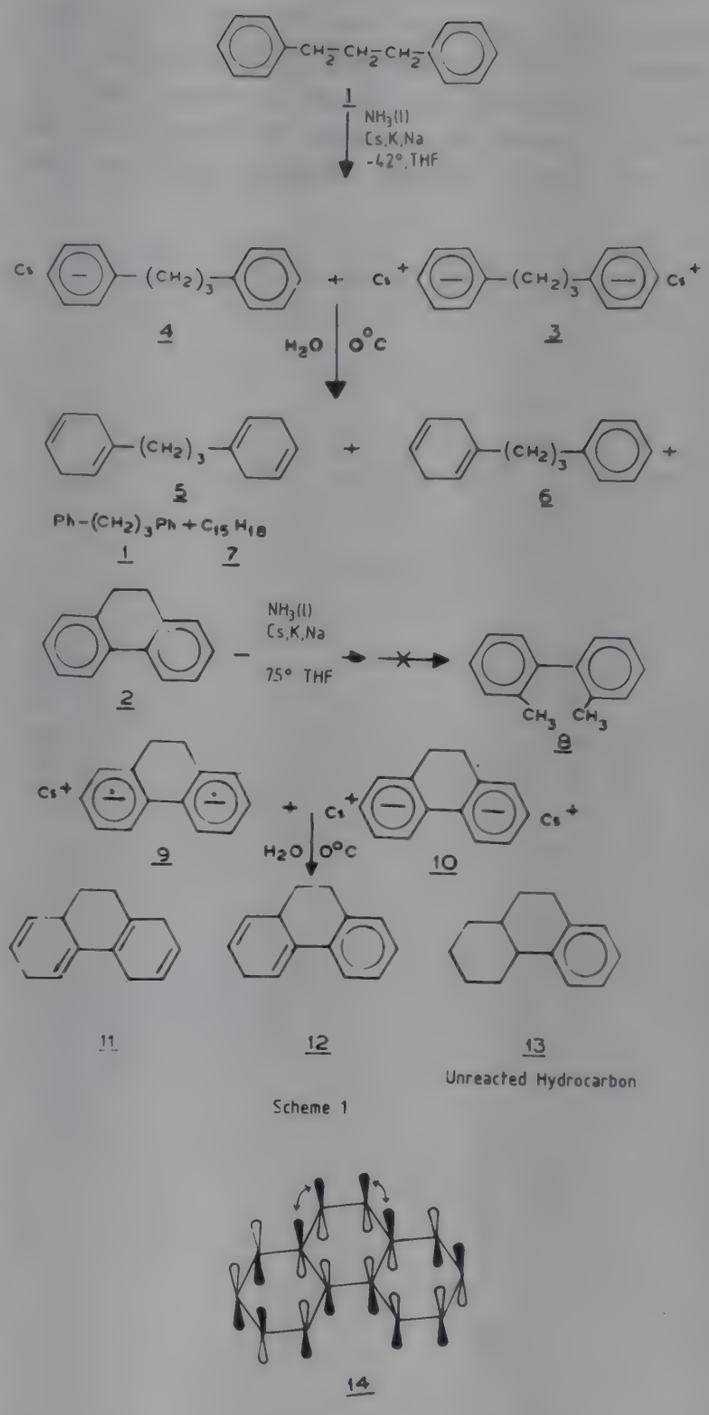
1,3-Diphenylpropane (**1**) and 9,10-dihydrophenanthrene (**2**) on treatment with Cs-K-Na alloy in liquid ammonia give the ring reduction products. The reduction takes place through mono and diradical anions.

In our earlier communications[1,2] we have shown that diphenylmethane and 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptane on treatment with Cs-K-Na alloy in liquid ammonia undergo metallation instead of either ring fusion or cleavage reaction. In this note we wish to report an entirely different reaction sequence for 1,3-diphenylpropane (**1**) and 9,10-dihydrophenanthrene (**2**) on treatment with Cs-K-Na alloy.

The reaction of **1** with cesium alloy was similar to that of diphenylmethane in that only ring reduction products were obtained. Thus, hydrolysis of the products from the reaction of **1** with Cs-K-Na alloy at −42° for 21 hr gave mainly 1,3-bis(2,5-dihydrophenyl)-propane (**5**) (31.8mol%) and 1-(2′,5′-dihydrophenyl)-3-phenylpropane (**6**) (33.5 mol %). Since the radical yield as measured by ESR spectroscopy was 31.5% (based on the available number of aromatic rings) and quenching with iodine resulted in a quantitative recovery of **1**, the reaction must be taking place through radical anions **3** and **4** (Scheme 1).

Similar is the case with 9,10-dihydrophenanthrene (**2**) which also gave only the ring reduction products other than the expected cleavage product 2,2′-bitolyl (**8**). This could be due to the formation of mono and diradical anions **9** and **10** (Scheme 1).

The reaction was carried out using 4.762 mmol of **2** and 19.075 mmol of cesium at −75° for 2 hr. Equal portions of the reaction mixture were then siphoned separately onto cold water and cold D_2O. The extracted mass from each work-up was subjected to GLC-mass spectral analysis. GLC was run on a OV17 (6′,1/8″) column at 160° (isothermal). The D_2O quenched portion gave six peaks at RRT 3.3, 3.5, 4.7, 6.4, 7.6 and 9.6 min with M^+ at *m/z* 188, 188, 188, 180, 184 and 182 respectively. The water quenched portions also gave six peaks at RRT 3.0, 3.4, 3.7, 4.7, 5.7, 6.2 min with M^+ at *m/z* 188, 186, 186, 186, 180 and 184 respectively. The most likely structures derivable from these results could be **11**, **12** and **13**.



Scheme 1

In order to prove that no cleavage occurred in the $-CH_2-CH_2-$ region, 100 mg of protonated dried mixture was dehydrogenated with 5% charcoal carbon. The PMR spectra of the product in CCl_4 exhibited signals at δ2.08 (4H, CH_2, *s*) and 6.6-7.8 (8H, Ar-*H*, *m*). These PMR data did notcoincide with those

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of 2,2'-bitotyl, and the product was identical with 9,10-dihydrophenanthrene (**2**) on TLC and GLPC.

The fact that 9,10-dihydrophenanthrene (**2**) does not undergo facile cleavage could be due to the rigid geometry of the molecule where the electron orbitals of aromatic ring can not efficientlp overlap the sp^3 orbitals of dimethylene linkage, and hence the bond can not cleave through electron repulsion (the unpaired diradical dianions of **2** could be in the HOMO **14**).

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Facile Cleavage of Bibenzyls by Cs-K-Na Alloy Leading to the Formation of Benzyl Carbanions

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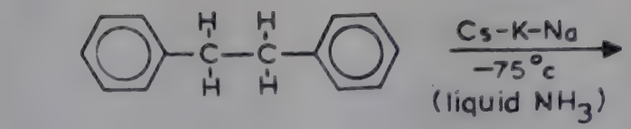
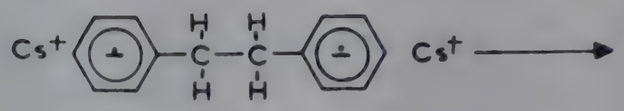
Facile cleavage of twelve substituted bibenzyls (1-12) with Cs-K-Na alloy at −75° leading to the formation of benzyl carbanions has been studied.

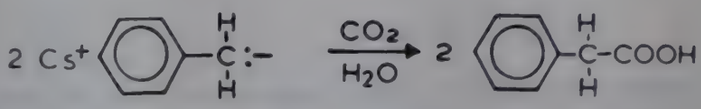
Reduction of aromatic hydrocarbons (Ar-Ar) often results in C−C bond cleavage[1]. The question is whether radical anion (Ar^-) or dianion (Ar^{2-}) is the species undergoing cleavage is often difficult to answer, because disproportionation of radical anions produces dianions, even if a small quantity of reducing agent is employed. If Ar^{2-} is more susceptible to cleavage than Ar^- the reaction can occur through the former even if it is present only in traces.

To our knowledge, the intermediacy of dianion has been unequivocally demonstrated in only one report on the reactions of this type. For the reductive cleavage of 1,2-di-(α-naphthyl)ethane to α-methylnaphthyl carbanions, Langendikj and Szwarc[2] observed a kinetic rate law which was second order in [Ar^-] and inversely proportional to [Ar], as required for dianion intermediacy.

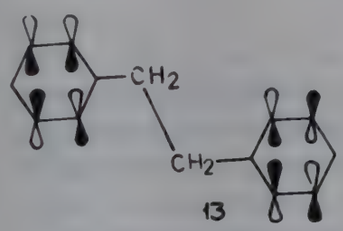
In the present report we wish to record similar type of observations in the case of 1,2-diphenylethane (**1**) and eleven of its methylated derivatives (**2-12**) which were cleaved with excess of Cs-K-Na alloy in liquid ammonia to give the corresponding benzylic anions in quantitative yields. Thus, these compounds (**1-12**) instead of undergoing intramolecular cyclization or side chain metallation[3,4] with Cs-K-Na alloy at −75 formed a diradical anion which then underwent cleavage to benzylcesium (Scheme 1). This was confirmed by carbonating the product to yield the corresponding phenylacetic acids and and also by quantitative analysis of their methyl esters by GLC. The cleavage of bibenzyl diradical anion can be rationalised by the observation that the unpaired electrons in the diradical anion could be in HOMO **13** or **14**. In **14** an electron rich *p*-orbital can overlap sp^3 bonding orbitals of the dimethylene linkage resulting







Scheme 1



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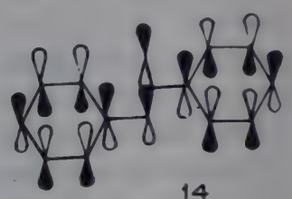

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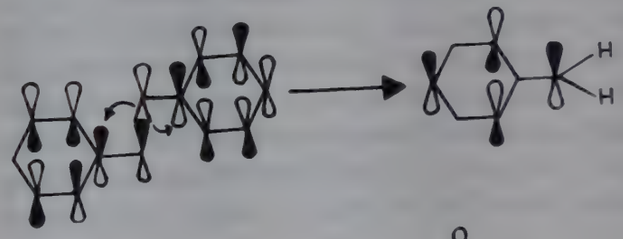

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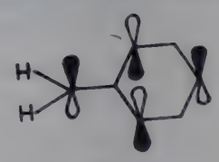

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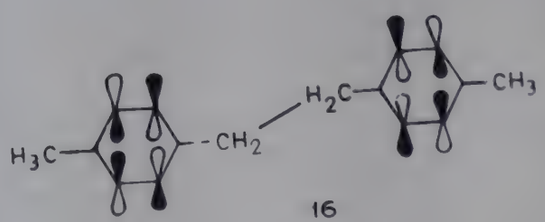

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in bond cleavage through electron repulsion. The net result would be to move an electron from an antibonding orbital of the radical anion to a non-bonding orbital giving the benzyl anion **15**.

This mechanism was observed in all the mono and disubstituted bibenzyls (**1-11**) except in the case of 4,4'-dimethylbibenzyl (**12**) which gave only 6.2 mol % yield

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Table 1—Results of the Reactions of Bibenzyls (1-12) with Cs-K-Na Alloy in Liquid Ammonia (−75°) for 2 hr

Sl No	Bibenzyl used	Amount (mmol)	Cs used (mmol)	Acid formed (mmol)
1	Bibenzyl (1)	2.972	9.87	Methyl benzylacetate (5.79)
2	2-Methylbibenzyl (2)	2.956	9.81	Methyl 2-methylphenylacetate (2.75) and methylphenylacetate (2.60)
3	2,2′-Dimethylbibenzyl (3)	3.356	13.382	Methyl 2-methylphenylacetate (6.594)
4	3,3′-Dimethylbibenzyl (4)	2.52	9.885	Methyl 3-methylphenylacetate (4.462)
5	3-Methylbibenzyl (5)	9.05	34.56	Methyl 3-methylphenylacetate (8.667) and methylphenylacetate (8.953)
6	4-Methylbibenzyl (6)	5.46	18.35	Methyl 4-methylphenylacetate (5.39) and methylphenylacetate (5.23)
7	3,5,3′,5′-Tetramethylbibenzyl (7)	2.1126	10.647	Methyl 3,5-dimethylphenylacetate (4.1524)
8	2,6,2′,6′-Tetramethylbibenzyl (8)	2.189	11.47	Methyl 2,6-dimethylphenylacetate (4.287)
9	α,α′-Dimethylbibenzyl (9)	3.1426	12.425	Methyl a-methylphenylacetate (6.2670)
10	α,α,α′α′-Tetramethylbibenzyl (10)	2.175	11.42	Methyl a,a′-dimethylphenylacetate (4.52)
11	2,6-Dimethylbibenzyl (11)	2.579	10.325	Methyl 2,6-dimethylphenylacetate (2.523) and methylphenylacetate (2.482)
12	4,4′-Dimethylbibenzyl (12)	2.46	9.385	Methyl 4-methylphenylacetate (—)

All the compounds were routinely checked on a 6′ × 1/4″ 10% carbowax 'M on 60/80 chromosorb W GLC column at 150 (isothermal temperature) as their methylesters. These compounds were separated on preparative GLC and were checked by PMR and mass spectra.

of *p*-tolylacetic acid at −75° in 2 hr. Increase in reaction period however gave better yield of *p*-tolylacetic acid (the main products in this reaction were noncleaved Birch reduction products, the chemistry of which will be published elsewhere). The resistance of **12** to undergo cleavage can not be ascribed to its failure to form the diradical anion. However, *p*-methyl groups would destabilize the 4,4′-dimethyl derivative of MOOH **14** considerably, since these are located on carbons of highest spin density. Thus, the most stable diradical anion of **12** would be HOMO **16**. Since the electron spin density in the HOMO **16** can not overlap the sigma orbital of dimethylene linkage, the molecule would not undergo facile cleavage to give two *p*-methylbenzyl anions. The results are given in Table 1.

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Novel Dimerisation Reaction of Hydrocarbons with Cs-K-Na Alloy

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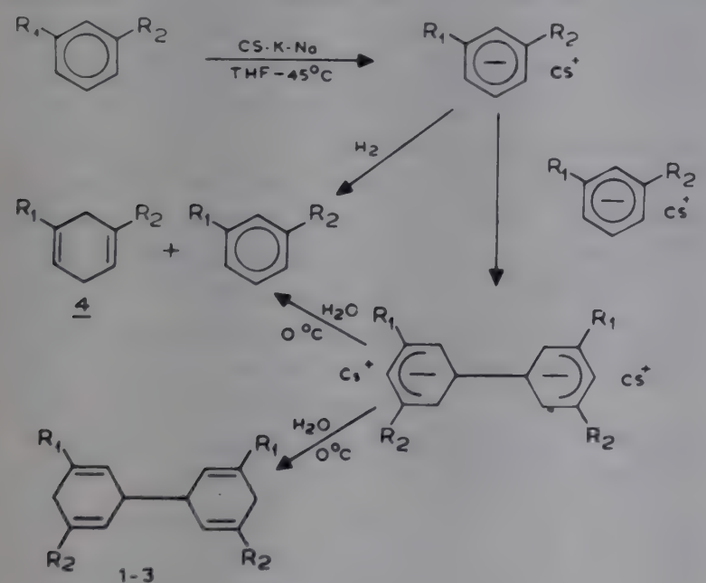
m-Xylene undergoes dimerisation with Cs-K-Na alloy at −48° to give 1,1′,4,4′-tetrahydro-3,3′,5,5′-tetramethylbiphenyl (3) while *o*- and *p*-xylenes do not follow such a reaction under identical conditions.

Earlier we have reported[1] the novel dimerisation reaction of benzene and toluene with Cs-K-Na alloy to give 1,1′,4,4′-tetrahydrobiphenyl (**1**) and 1,1′,4,4′-tetrahydro -3,3′-dimethylbiphenyl (**2**) in good yields alongwith other products. The above reaction has now been extended to *m*-xylene, *o*-xylene, *p*-xylene and *t*-butylbenzene.

Like benzene and toluene, *m*-xylene react with excess Cs-K-Na alloy in THF at −48°C to give the *m*-xylene radical anion which mainly dimerises. Thus, after protonation, 1,1′,4,4′-tetrahydro-3,3′,5,5′-tetramethylbiphenyl (**3**) is obtained in 55 mol % yield alongwith *m*-xylene (28 mol %) and 2,5-dihydro-*m*-xylene (**4**; 13 mol %). Thus, the dimerisation of cesium

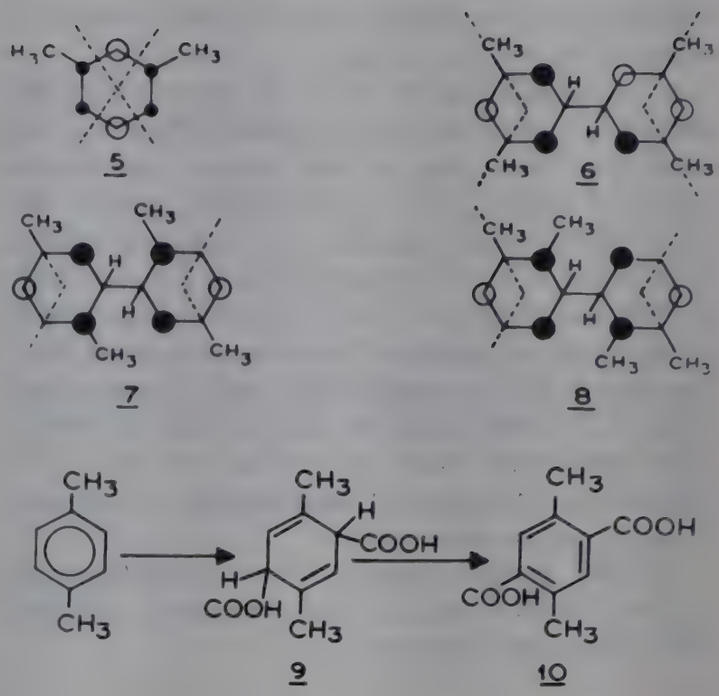


1-3

3, **4** ---- $R_1 = R_2 = CH_3$

2 ---- $R_1 = CH_3, R_2 = H$

1 ---- $R_1 = R_2 = H$



5 **6** **7** **8** **9** **10**

m-xylenide favours coupling at position *meta* to both methyl groups. This can be understood since dimerisation of *m*-xylene radical anion (i.e. HOMO structure **5**) is expected to take place at the position of highest spin density. In the present study dimerisation of *m*-xylene radical anion takes place at a position *meta* to both methyl groups since this process leads to the most stable anion **6** when the methyl groups are at the nodal positions in the HOMO (and hence destabilise the anion as little as possible).

Unlike *m*-xylene, *p*-xylene does not react with excess Cs-K-Na alloy at −45° in THF to give the dimerised product. This may be due to the fact that the HOMO anion **7** formed by dimerisation of the *p*-xylene radical anion is destabilised by the two methyl groups on carbons bearing excess negative charge. *o*-Xylene also does not dimerise due to destabilisation of the HOMO anion **8** of *o*-xylene radical anion by the two methyl groups on carbons bearing excess negative charge. Protonation of the reaction mixture in both cases give the starting meterial alongwith traces (1%) of a dihydro compound.

However, the carbonation experiment on *p*-xylene at −75° with excess of Cs-K-Na alloy leads to the formation of 1,2,4,5-tetrahydro-*p*-xylene-3,6-dicarboxylic acid (**9**) in 72% yield; PMR ($CDCl_3$): 1.4, 2.65 (6H, *s*, 2 × CH_3), 3.80 (6H, *s*, 2-and 6-$COOCH_3$) 7.10 (2H; *s*, vinylic protons). It was converted into *p*-xylene -2,6-dicarboxylic acid (**10**) via dehydrogenation with 5% Pd/C, yield 93%; PMR (CCl_4) of dimethyl ester: 2.5 (6H, *s*, 1- and 4-CH_3), 3.81 (6H, *s*, 2- and 6-CO_2CH_3), 7.66 (2H, *s*, Ar-*H*).

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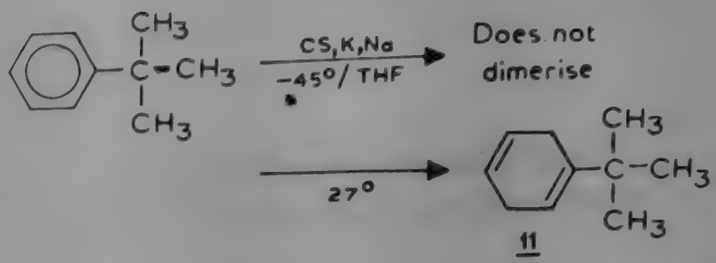
The above experiment definitely proves the formation of radical anion[2].

Unlike toluene, *t*-butylbenzene does not react with excess of Cs-K-Na alloy in THF at $-45°$. This is not surprising since *t*-butylbenzene is 25 times less stable as a radical anion than toluene[3].

It is presumed that at $-45°C$ the distance from the surface of cesium cation to the plane of benzene ring could be 1.31Å. Even at this distance, the cesium cation of radius 2.45Å would slightly overlap the bulky *t*-butyl group. However, as the temperature is raised from $-45°$ to 25° the effective radius of cesium in THF decreases from 2.45Å to 2.25Å. This would eliminate the interaction of the cesium cation and the *t*-butyl group and may explain why *t*-butylbenzene does react at 27°C with Cs-K-Na alloy in THF to form a black precipitate which on protonation gives 2,5-dihydro-*t*-butylbenzene (**11**) and the dimer **12** in **13** and 1 mol, % yields respectively.

All the reaction products were quantitatively analysed by GLC on a $6' \times 1/4''$ carbowax 20M on 60/80 chromosorb column.



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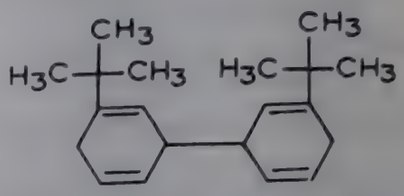

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Claisen Condensation of Phthalides with Diethyl Oxalate: Formation of 3-Carbethoxy-4-hydroxyisocoumarins via Rearrangement

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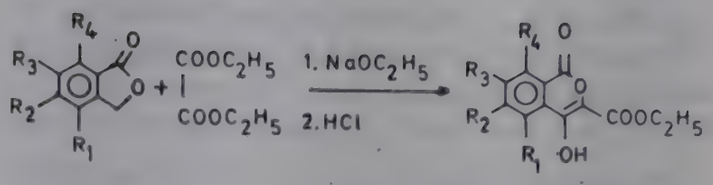
The structure of sodium ethoxide-catalysed condensation product of 4,5,6-trimethoxyphthalide (**1a**) with diethyl oxalate has been revised as 3-carbethoxy-4-hydroxy-5,6,7-trimethoxyisocoumarin (**2a**) instead of 3-carbethoxyformyl-4,5,6-trimethoxyphthalide (**3**). The preparation of 3-carbethoxy-4-hydroxyisocoumarins (**2b-d**) by a similar condensation of phthalides (**1b-d**) has also been described.

3-Carbethoxyformyl-4,5,6-trimethoxyphthalide (**3**) was required for a different investigation. Its preparation has been described by King *et al.*[1] by the condensation of 4,5,6-trimethoxyphthalide (**1a**) with diethyl oxalate in benzene in the presece of sodium ethoxide. On repeating the experiment, a compound, m.p. 188°, raised to 193-94° after crystallisation from acetic acid (reported m.p. 188-89°) was obtained which had the same elemental composition ($C_{15}H_{16}O_8$) as **3**. It gave a steel blue colour with ferric chloride and exhibited IR absorptions at 1735 (lactone), 1665 (ester, chelated) and 1620 cm^{-1} (double bond). The PMR spectrum of the compound in $CDCl_3$ displayed signals at δ 1.43 (t, $J=7$ Hz, 3H, $-COOCH_2CH_3$); 3.94 (s, 3H, 6-OCH_3), 4.02 (s, 3H, 7-OCH_3), 4.03 (s, 3H, 5-OCH_3), 4.34 (q, $J=7$ Hz, 2H, $-COOCH_2CH_3$), 7.7 (s, 1H, 8-H) and 11.28 (s, 1H, $-OH$, exchangeable with D_2O). On treatment with acetic anhydride in the presence of pyridine, it formed an acetate (m.p. 145°) which exhibited IR absoorptions at 1775 (enol acetate), 1735 (lactone), 1720 (ester) and 1615 cm^{-1} (double bond). On the basis of above spectral data, the structure of the compound was revised to 3-carbethoxy-4-hydroxy-5,6,7-trimethoxyisocoumarin (**2a**).

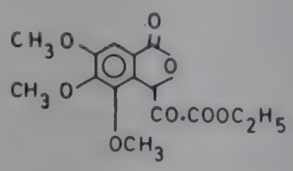
A similar condensation of phthalides (**1b-d**) with diethyl oxalate gave 3-carbethoxy-4-hydroxyisocoumarins (**2b-d**; Table 1). 3-Carbethoxy-4-hydroxy-6,7-dimethoxyisocoumarin (**2c**) on acid-catalysed hydrolysis afforded 3,4-dihydro-4-keto-6,7-dimethoxyisocoumarin (**4**) identical with that prepared by the known procedure[2]. This further confirmed the proposed structure (**2**) for the condensation products.

Similar preparations of the 3-carbethoxy-4-hydroxyisocoumarins **2e** and **2f-h** have been reported by Molho *et al.*[5] and Narasimhan *et al.*[6] respectively



(1) (2)

a: $R_1=R_2=R_3=OCH_3$, $R_4=H$
b: $R_1=R_3=OCH_3$, $R_2=R_4=H$
c: $R_1=R_4=H$, $R_2=R_3=OCH_3$
d: $R_1=R_2=OCH_3$, $R_3=R_4=H$
e: $R_1=R_2=R_3=R_4=H$
f: $R_1=OCH_3$, $R_2=R_3=R_4=H$
g: $R_1=R_3=R_4=H$, $R_2=OCH_3$
h: $R_1=R_2=R_4=H$, $R_3=OCH_3$



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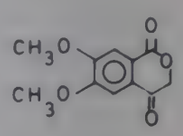

(4)

Table 1—Characterisation Data of 3-Carbethoxy-4-hydroxyisocoumarins

Phthalide used	Reaction conditions	Product*	Yield (%)	m.p.† °C
1a[1]	Benzene, reflux, 2 hr	**2a**	25	193-94
1b[3]	Benzene, RT, 10 hr	**2b**	20	199
1c[4]	Benzene, RT, 12 hr	**2c**	30	228
1d[4]	Ether, RT, 10 hr	**2d**	20	149

*All the compounds gave satisfactory C, H analyses and PMR data. †Compounds **2a-c** were crystallised from acetic acid and **2d** was crystallised from benzene.

M.ps are uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer 237 spectrophotometer and PMR spectra in $CDCl_3$ on 90 MHz and 60 MHz instruments using TMS as internal standard.

3-Carbethoxy-4-hydroxyisocoumarins (**2a-d**)

To a suspension of powdered sodium ethoxude [prepared from sodium (575 mg, 25 mmol)] in dry ether (50 ml), a solution of **1** (12.5 mmol) in dry benzene (70 ml) containing freshly distilled diethyl oxalate (3.65 g, 25 mmol) was added dropwise with stirring in the cold. The reaction mixture was then stirred at room temperature for the period indicated in Table 1. Usual work-up afforded the related hydroxyisocoumarins.

3,4-Dihydro-4-keto-6,7-dimethoxyisocoumarin (**4**)

Compound **2c** (250 mg, 0.85 mmol) was refluxed with a mixture of acetic acid (6 ml) and conc.

hydrochloric acid (4 ml) for 4 hr. The reaction mixture was concentrated under reduced pressure and cooled to give **4** which crystallised from ethanol as light brown needles (100 mg, 53%), m.p. 245-46°, identical (m.m.p. and IR) with a specimen prepared following the literature method[2] (reported m.p. 246°); IR (KBr): 1720 (lactone carbonyl) and 1675 cm^{-1} (ketone) (Found: C, 59.2; H, 4.7. Calc. for $C_{11}H_{10}O_5$: C, 59.4; H, 4.5%).

The author expresses his sincere thanks to the Head, Department of Chemistry, Patna University, Patna for providing necessary facilities and to Prof J N Chatterjea for his interest.

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Photocycloaddition of Tetracyanoethylene to 4-Benzalamino-5-styrylisoxazoles

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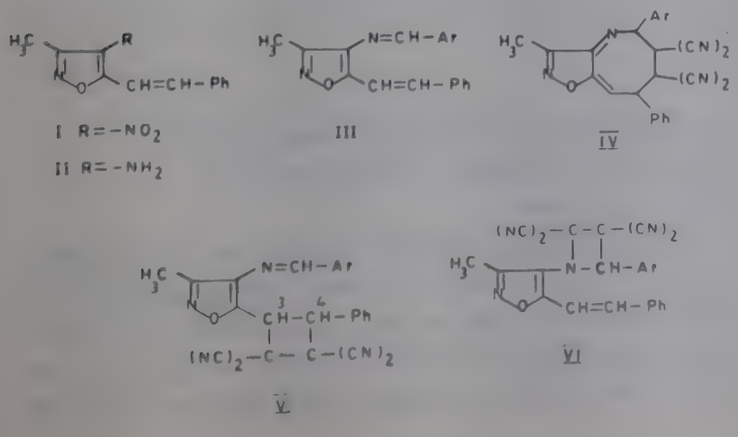
Photolysis of 4-benzalamino-3-methyl-5-styrylisoxazoles (III) and tetracyanoethylene provides only the substituted cyclobutanes (V) though azetidines (VI) and azocines (IV) are also possible.

As a part of our project to carry out pericyclic reactions on isoxazoles, we have reported recently the first ever electrocyclization of isoxazole schiff bases[1]. In continuation of our interest in the same direction we have now investigated the photocycloaddition on isoxazoles with tetracyanoethylene. Most of the tetracyanoethylene reactions are reported to involve charge transfer complex formation, which is the outstanding characteristic feature of this highly π-deficient molecule. The cycloaddition reactions of this compound are comparatively few and sporadic[2-5]. We report herein for the first time the cycloaddition of tetracyanoethylene on isoxazoles.

4-Benzalamino-3-methyl-5-styrylisoxazoles (III) required for the cycloaddition were prepared starting from 3, 5-dimethylisoxazole. Nitration of the latter with nitric acid-sulphuric acid[6] and subsequent regioselective styrylation with benzaldehyde in the presence of piperidine furnished 3-methyl-4-nitro-5-styrylisoxazole[7] (I, R = NO_2). Reduction of I with stannous chloride-hydrochloric acid[7] gave 4-aminoisoxazole (II) which on condensation with various benzaldehydes in refluxing ethanol afforded the isoxazole schiff bases (III)[8,9]. The photocycloaddition was carried out by stirring tetracyanoethylene and III in tetrahydrofuran at 5°C in bright sunlight for 1 hr. Removal of solvent followed by trituration of the resulting gum with methanol gave a solid. This reaction being a photochemical process, according to Woodward-Hoffmann rules, should involve a supra-supra addition and is expected to give the adduct(s) IV[6 + 2], V[2 + 2] or/and VI[2 + 2]. The schiff bases (III) gave 3-(4-arylideneamino-3-methyl-5-isoxazolyl-1, 1, 2, 2-tetracyano-4-phenylcyclobutanes (V, Table 1) as the sole products, though in low yields.



The structures of the cyclobutanes (Va-f) were established by elemental analyses, IR spectra exhibiting νCN at 2260 cm^{-1}, PMR and mass spectra (M^+ m/z 416). The IR spectra of V did not show an absorption at 970 cm^{-1} due to −CH bending of −CH =CH− present in the precursor indicating that the styryl double bond had disappeared due to cycloaddition. The most significant feature of the PMR spectra of V is the appearance of two doublets at δ 5.75 (1H, J = 12Hz, H-4) and 6.25 (1H, J = 12Hz, H-3) due to the two tertiary protons of the newly formed cyclobutane ring. The same protons in the starting compound resonated in the aromatic region (δ 7.0-7.3) as an AB quartet. The chemical shift of the azomethine proton remained unaffected ruling out the formation of IV and VI.

The very low intensity (1.5%) of the molecular ion peak of the cycloadduct (V) is in keeping with the fact that it contains four highly electron withdrawing groups (−CN). A notable feature of the mass spectrum is the unusually higher intensity of the (M + 1) peak than the calculated value based on isotopic contribution. This is probably due to the bimolecular collision between the molecular ion and a neutral molecule leading to the abstraction of a hydrogen atom from the latter by the former resulting in **A** (Chart 1), a mass spectral behaviour shown also by ethers[10]. The base peak at m/z 131 due to cinnamoyl cation resulting from **B** is a consequence of typical mass spectral behaviour of isoxazoles whose N−O bond is most readily cleaved leading to the formation of azirines and expulsion of 5-substituent as acyl fragment[11]. The peak at m/z 157 can be ascribed to the azirine (**C**) which is again formed by a typical isoxazole fragmentation. The cyclobutane fragment ion (**D**) at m/z 154 provides an additional evidence in favour of the cycloaddition of tetracyanoethylene to styryl double bond rather than on azomethine linkage.

The reaction when conducted in the absence of light did not proceed indicating it to be a pericyclic process. This is in conformity with the fact that [2 + 2] cycloadditions are thermally forbidden.

Table 1—Characterisation Data of Isoxazolylcyclobutanes (V)

Compd	Ar	m.p.* °C	Mol. formula	Found (%) (Calc.) C	H	N	PMR (DMSO-d_6), δ ppm
Va†	Phenyl	210	$C_{25}H_{16}N_6O$	72.1 (72.1	3.8 3.8	20.0 20.2)	3.45 (3H, *s*, CH_3), 5.75 (1H, *d*, J=12Hz, H-4), 6.25 (1H, *d*, J=12Hz, H-3), 7.5-8.1 (10H, *m*, Ar−*H*), 8.9 (1H, *s*, −CH=N)
Vb	*p*-Tolyl	198	$C_{26}H_{18}N_6O$	72.3 (72.6	4.2 4.2	19.4 19.5)	—
Vc‡	*p*-Methoxyphenyl	195	$C_{26}H_{18}N_6O_2$	69.7 (70.0	4.0 4.0	18.5 18.8)	3.42 (3H, *s*, CH_3), 3.92 (3H, *s*, OCH_3), 5.6 (1H, *d*, J=12Hz, H-4), 6.1 (1H, *d*, J=12Hz, H-3), 7.2-8.0 (9H, *m*, Ar−*H*), 8.7 (1H, *s*, −CH=N)
Vd**	*p*-Chlorophenyl	202	$C_{25}H_{15}N_6OCl$	66.4 (66.7	3.1 3.3	18.6 18.7)	3.48 (3H, *s*, CH_3), 5.8 (1H, *d*, J=12Hz, H-4), 6.38 (1H, *d*, J=12Hz, H-3), 7.6-8.5 (9H, *m*, (Ar−*H*), 9.1 (1H, *s*, −CH=N)
Ve	*p*-Dimethyl-aminophenyl	240	$C_{27}H_{21}N_7O$	71.1 (70.6	4.5 4.6	21.3 21.4)	—
Vf	*p*-Nitrophenyl	215	$C_{25}H_{15}N_7O_3$	65.2 (65.1	3.3 3.	21.1 21.3)	—
Vg	*p*-Hydroxyphenyl	206	$C_{25}H_{16}N_6O_2$	68.8 (69.4	3.7 3.7	19.3 19.4)	
Vh	*p*-Hydroxy-*m*-methoxyphenyl	186	$C_{26}H_{18}N_6O_3$	67.4 (67.5	3.8 3.9	18.1 18.2)	—
Vi	*m*-Bromophenyl	165	$C_{25}H_{15}N_6OBr$	60.0 (60.6	3.1 3.0	17.2 17.0)	—
Vj	α-Thienyl	171	$C_{23}H_{14}N_6OS$	65.4 (65.4	3.1 3.3	20.1 19.9)	—

*All the compounds crystallized from pet. ether-benzene.
†IR: 2260 (−C≡N), 1615 (>C=N), 1580 (−CH=N−).
‡IR: 2265 (−C≡N), 1615 (>C=N), 1585 (−CH=N−).
**IR: 2270 (−C≡N), 1610 (>C=N), 1580 (−CH=N−).

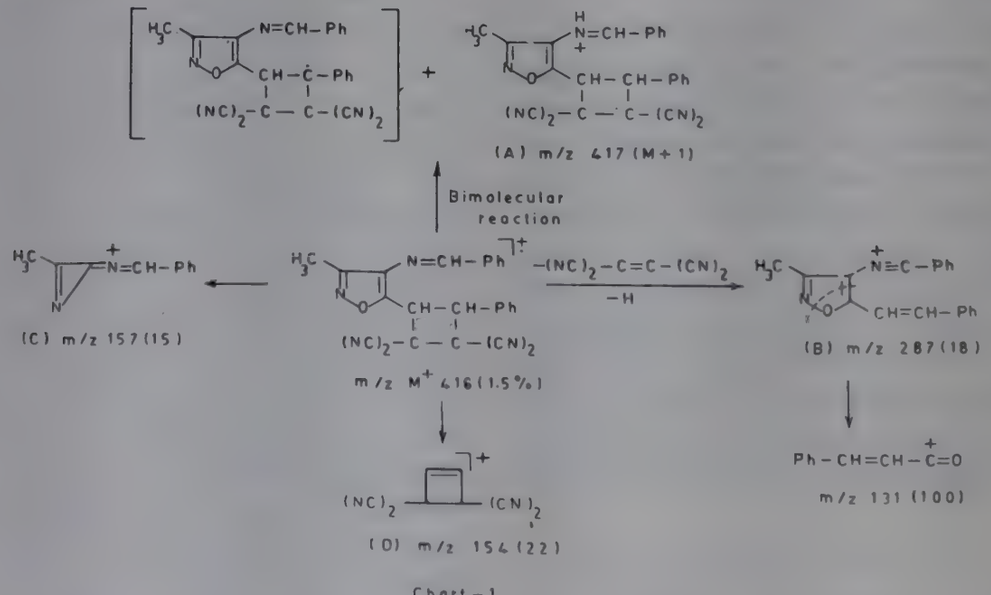


Chart-1

All the melting points reported are uncorrected. Purity of the compounds was checked by TLC. The IR spectra were run in KBr on a Perkin-Elmer 283 model (ν_{max} in cm^{-1}), 90 MHz PMR spectra in DMSO-d_6 on a Varian EM-390 spectrometer using TMS as the internal reference (chemical shifts in δ, ppm) and the mass spectra on a Varian MAT CH-7 instrument at 70 eV.

3-(4-Benzalamino-3-methyl-5-isoxazolyl)-1,1,2,2-tetracyano-4-phenylcyclobutanes (V):
General procedure

The appropriate 4-benzalamino-3-methyl-5-styryl-isoxazole[8] (III; 0.01 mol) and tetracyanoethylene (0.01 mol) were taken in tetrahydrofuran (50 ml), and the mixture was stirred at 0° in bright sun light for 1 hr. The gummy product obtained after the removal of the

solvent at ambient temperature was triturated with methanol and the product recrystallized from pet. ether-benzene to get white shining crystals of V (Table 1).

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Ring Opening & Transamination of Pyridinium Salts

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N-Alkyl-3-cyanopyridinium iodides (Ia-c) undergo ring opening and recyclization when heated with aq. alkyl amine to give 2-alkylamino-3-formylpyridines (IIa-c) and 3-cyanopyridine (III). However, when compounds Ia-c are treated with alkyl amines in which the alkyl radical is different from that in I, recyclization and transamination reactions take place to give II.

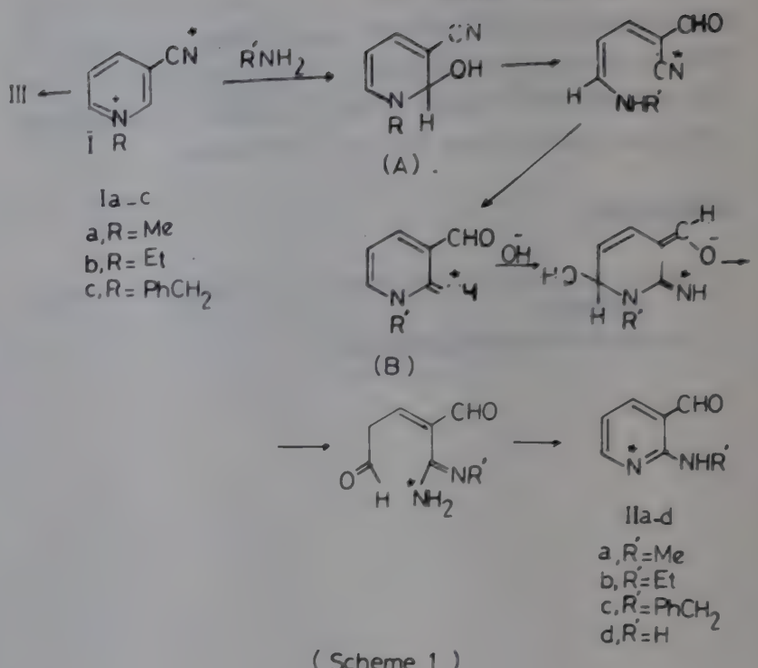
In continuation of our current research work on recyclization and isomerisation of pyridinium salt[1-6], we report herein the effects of cyano group as well as of various amines on the recyclization of such compounds.

N-alkyl-3-cyanopyridinium iodides (Ia-c) when heated with an aq. alkyl amine (35%), in which the alkyl group was similar to that in the pyridinium salt, gave 2-alkylamino-3-formylpyridines (IIa-c) in good yields.

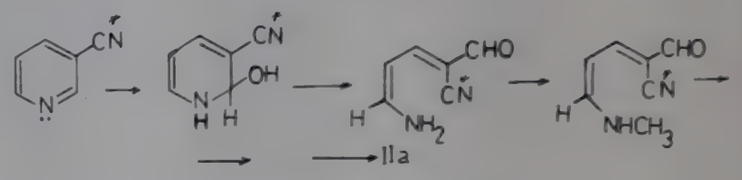
The reaction is supposed to proceed via the formation of δ-complex (**A**) which on ring opening and recyclization gives the substituted 1,2-dihydropyridine (**B**). The latter (**B**) under the reaction conditions undergoes rearrangement, similar to that described for the amidine rearrangement[7,8], to give 2-alkylamino-3-formylpyridine (II) (Scheme 1) in 50-56% yield.

However, N-alkyl-3-cyanopyridinium salts (I), when treated with aq. alkyl amines in which the alkyl group is different from that in I, undergo recyclization and transamination reactions[2,9]. Thus, the reaction of aq. methyl amine with N-ethyl- and/or N-benzyl-3-cyanopyridinium iodide (Ib,c) led to the formation of 2-methylamino-3-formylpyridine (IIa) in 51-57% yield along with 3-cyanopyridine (III) in 14% yield. Similarly, aq. ethyl amine on reaction with N-methyl and/or N-benzyl-3-cyanopyridinium iodide (Ia-c) gave 2-ethylamino-3-formylpyridine (IIb) in 47-53% yield as a result of reamination reaction, and III through N-dealkylation of I.

On the other hand, the reaction of aq. benzyl amine with N-methyl and/or N-ethyl-3-cyanopyridinium salt (Ia,b) afforded 2-methylamino- and/or 2-ethylamino-3-formylpyridine (IIa,b) as the main product in 47-53% yield, and 2-benzylamino-3-formylpyridine (IIc) which was expected as the main product was not detected in the PRM spectrum. However, the GLC-mass spectrum showed that compound IIc was formed in a very poor yield. This reaction also gave compound III in 10% yield.



(Scheme 1)



(Scheme 2)

Treatment of Ia with aq. dimethyl amine gave IIa and III in 10% and 45% yields respectively indicating that the secondary amine (Me_2NH) was not involved in the reamination reaction.

Based on the evidence that treatment of N-alkylpyridinium salts with aq. ammonia or ammonium sulphite[10,11] leads to dealkylation only, it seemed of interest to study the action of ammonium salt solution on Ia. In such a reaction the recyclization reaction was found to occur with the exchange of methylamino function by amino group, and the reaction products were IIa (8% yield), III (45% yield) and 2-amino-3-formylpyridine (IId) (6% yield).

It was also interesting to study the recyclization of unquaternized 3-cyanopyridine (III). When III was heated with methyl amine solution, recyclization occurred with the formation of IIa (Scheme 2) in 13% yield. The yield of this product was enhanced by using zinc chloride as a catalyst[3,6].

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Melting points are uncorrected. The reaction products were shown to be homogeneous by TLC (benzene). The PMR spectra were recorded in CCl_4 on a Varian T-60 instrument with TMS as internal standard (chemical shifts in δ, ppm), UV spectra in ethanol on a Cary-219 spectrophotometer (λ_{max} in nm), IR spectra in KBr on an UR-20 spectrophotometer (ν_{max} in cm^{-1}), mass spectra on an MX-1303 mass spectrometer at 50 eV, and GC-mass spectra on a Varian instrument at 80 eV using a column (1.5 m × 3.5 mm) containing SE-30 (15%), at temperature 100-250°.

N-Alkyl-3-cyanopyridinium salts (Ia-c)

A mixture of 3-cyanopyridine (0.02 mol) and the alkyl halide (0.03 mol) was heated in a sealed tube at 110° for 15-30 hr. The product was isolated as yellow crystals from ethanol-ether (3:1). The characterization data of Ia-c thus prepared as follows:

Ia: Yield 80%, m.p. 190° (Found: C, 34.2; H, 2.7. $C_7H_7N_2I$ requires C, 34.2; H, 2.9%).

Ib: Yield 85%, m.p. 188° (Found: C, 37.1; H, 3.6. $C_8H_9N_2I$ requires C, 36.9; H, 3.5%).

Ic: Yield 60%, m.p. 210° (Found: C, 48.1; H, 3.4. $C_{13}H_{11}N_2I$ requires C, 48.4; H, 3.4%).

Recyclization of N-alkylcyanopyridinium salts (Ia-c) to 2-alkylamino-3-formylpyridines (IIa-c): General procedure

To I (0.01 mol) was added 22 ml of the aq. solution (35%) of an appropriate alkylamine and the mixture heated in a sealed tube at 150° for 22 hr. The product was extracted with ether, dried and chromatographed over silica gel (L 100/160 μ). The eluent was removed under reduced pressure to give II, the characterization data of which are as follows:

Compound IIa: Yield 64%; IR: 3355 (NH), 1675 (C=O), 2745 (aldehyde C−H); UV: 260, 365 (log ε 3.5, 3.4); PMR: 9.5 (*s*, CHO), 8.0 (*s*, NH), 7.8 (*m*, H-6, $J_{5,6}$ = 5 Hz, $J_{4,6}$ = 2 Hz), 7.2 (*m*, H-4, $J_{4,5}$ = 7 Hz, $J_{4,6}$ = 2 Hz), 6.2 (*m*, H-5, $J_{5,6}$ = 5 Hz, $J_{4,5}$ = 7 Hz), 2.8 (*d*, NCH_3, J_{NH,CH_3} = 5 Hz); MS: *m/z* 136 (30%), 108(40), 80(50), 79(100), 78(20), 57(11), 54(30), 52(30), 51(20).

Compound IIb: Yield 60%; IR: 3350 (NH), 1665(C=O), 2750 (aldehyde C−H); UV: 260, 365 (log ε 3.73, 3.71), PMR: 9.5 (*s*, CHO), 8.1 (*s*, NH), 8.0 (*m*, H-6, $J_{5,6}$ = 5 Hz, $J_{4,6}$ = 2 Hz, 7.2 (*m*, H-4, $J_{4,5}$ = 7 Hz, $J_{4,6}$ = 2 Hz) 6.1 (*m*, H-5, $J_{5,6}$ = 5 Hz, $J_{4,5}$ = 7 Hz), 3.5 (*m*, CH_2, J_{NH,CH_2} = 5 Hz, J_{CH_3,CH_2} = 7 Hz), 1.0 (*t*, CH_3, J_{CH_3,CH_2} = 7 Hz), MS: *m/z* 150 (30%), 135 (30), 108 (28), 107 (25), 94 (100), 79 (40), 78 (50), 67 (28), 52 (35), 51 (35).

Compound IIc: Yield 45%; IR: 3345 (NH), 1670 (C=O), 2750 (aldehyde C−H), UV: 263, 365 (log ε 3.68, 3.71); PMR: 9.5 (*s*, CHO), 8.1 (*s*, NH), 8.2 (*m*, H-6, $J_{5,6}$ = 5 Hz, $J_{4,6}$ = 2 Hz), 7.5 (*m*, H-4, $J_{4,5}$ = 7 Hz, $J_{4,6}$ = 2 Hz), 6.0 (*m*, H-5, $J_{5,6}$ = 5 Hz, $J_{4,5}$ = 7 Hz), 3.6 (*d*, NCH_2, J_{NH,CH_2} = 5 Hz), 6.4-7.5 (*m*, 8H, Ar−*H*); MS: *m/z* 212 (25%), 135 (27), 108 (30), 107 (20), 94 (100), 79 (30), 73 (55), 67 (30), 52 (30), 51 (38).

Effect of aq. ammonia on N-methyl-3-cyanopyridinium iodide (Ia)

To Ia (0.013 mol) was added aq. ammonia (20 ml), and the mixture heated for 35 hr in a sealed tube at 180°. The product was extracted with ether, the extract dried over magnesium sulphate and chromatographed over silica gel (L 100/160 μ) using benzene as eluent to give the following fractions:

Fraction − A: It gave compound IIa in 8% yield.

Fraction − B: It furnished 2-amino-3-formylpyridine (IId) in 6% yield; MS: *m/z* 122 (53%), 93 (100) 77 (10), 68 (5), 67 (10), 66 (45), 52 (15), 51 (15).

Fraction − C: It gave 3-cyanopyridine (III), m.p. 50° (Found: C, 69.0; H, 3.8; N, 26.6. Calc. for $C_6H_4N_2$: C, 69.3; H, 3.8; N, 26.9%).

Ring opening and recyclization of the pyridine base (III)

(A) Aqueous methylamine (20 ml) was added to III (0.01 mol) and the reaction mixture heated in a sealed tube for 60 hr at 180°. The product was extracted with ether, dried over magnesium sulphate and chromatographed over silica gel (L 100/160 μ) using benzene-ethyl acetate (4:1) as eluent to give compounds IIa and III in 13 and 54% yields respectively.

(B) The above reaction was repeated under identical conditions in the presence of zinc chloride (2 g). The products obtained were IIa and III.

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A Stereoselective Synthesis of Olefins by a New Semi-stabilized Phosphonium Ylide

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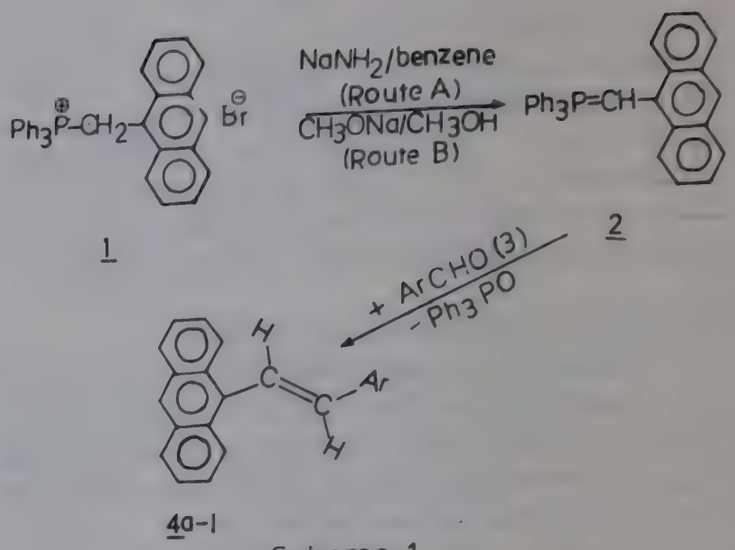
A new semi-stabilized phosphonium ylide, viz. (9-anthrylmethylene)triphenylphosphorane (**2**) generated by the action of sodium hydride or sodamide in benzene or sodium methoxide in methanol on (9-anthrylmethyl)triphenylphosphonium bromide (**1**), has been reacted with substituted aromatic aldehydes (**3**) to give exclusively the *trans*-1-(9-anthryl)-2-substituted-arylethylenes (**4**). The variation of solvents and bases has no effect on the stereoselectivity of the reaction. The *trans*-geometry of **4** has been established by IR and PMR spectral data.

The structural features of phosphonium ylides and aldehydes play an important role in determining the stereo-chemistry of the olefins formed in the reaction[1-7]. Thus, non-stable ylides when reacted with aromatic aldehydes, give a mixture of *cis*- and *trans*-olefins[8,9]. However, *trans*-olefins are the main products when stabilized ylides are used. But the reactions of semi-stabilized phosphonium ylides to give olefins are usually devoid of a marked stereoselectivity[10-12]. The electronic effects of substituents have also been found to influence the stereochemical nature of the reaction[13,14].

In continuation of our work on the reactivity and stereochemistry of various ylides of Vth group elements[16-21], we wish to report herein the reactions of a new semi-stabilized phosphonium ylide, (9-anthrylmethylene)triphenylphosphorane, with substituted aromatic aldehydes with a view to examining the effect of bulky anthracene ring in the geometry of the resultant ethylenes.

Quaternization of triphenylphosphine with 9-bromomethylanthracene in benzene at reflux temperature gave (9-anthrylmethyl)triphenylphosphonium bromide (**1**) in 70% yield. The action of sodium hydride in benzene or sodium methoxide in methanol on **1** generated an intense yellow colouration due to formation of the ylide (9-anthrylmethylene)triphenylphosphorane (**2**) which could not be isolated due to lack of stability under atmospheric conditions. Therefore, the reactions of **2** were carried *in situ*. The structure of the ylide **2** was derived from that of its precursor (**1**). The PMR spectrum of **1** exhibited a



Scheme 1

characteristic doublet due to $-CH_2-$ protons at δ 5.75 (J_{P-H} = 15 Hz) and a multiplet for aromatic protons in the range 7.10-8.42.

The ylide **2**, generated with NaH or $NaNH_2$ in benzene, underwent coupling reaction with aromatic aldehydes (**3a-l**) at reflux temperature to give *trans*-1-(9-anthryl)-2-arylethylenes (**4a-l**; Scheme 1) in 45-80% yields (route-A). Similarly when the ylide **2** was generated in methanol by sodium methoxide at room temperature and condensed with **3**, the *trans*-ethylenes (**4a-l**) were formed in 50-90% yields (route-B). The factors such as solvents and bases were incapable of changing the stereochemistry of the resultant **4**. However, the reaction was facile in a polar solvent and afforded **4** in better yields.

All the *trans*-ethylenes (**4a-l**; Table 1) had melting points in agreement with those reported in literature[15,17,22]. Their spectral data also supported the *trans*-geometry. The IR (KBr) spectra of **4** exhibited characteristic absorption bands at 1595-1620 (C=C) and 940-955 cm^{-1}. The later absorptions were associated with out-of-plane deformations of *trans*-hydrogens of the carbon-carbon double bond. The PMR ($CDCl_3$ using TMS) spectra of **4** in general exhibited *trans*-olefinic protons as a doublet in the range δ 6.90-7.63 (J = 15-17 Hz) and aromatic protons as a multiplet at 7.20-8.78.

(9-Anthrylmethyl)triphenylphosphonium bromide (**1**)

A solution of triphenylphosphine (50 mmol) and 9-bromomethylanthracene (50 mmol) in anhyd. benzene (500 ml) was refluxed under nitrogen atmosphere on a steam-bath for 8 hr, and cooled to room temperature. The resultant yellow solid was filtered and recrystallized from chloroform-ethylacetate to give microcrystals of **1** in 70% yield, m.p. 280-82° (Found:

Table 1—Characterization Data of *trans*-1-(9-Anthryl)-2-arylethylenes (**4a-l**)

Compd	Ar	m.p. (lit., m.p.) °C	Yield (%) Route A	Yield (%) Route B	Crystallized from	Found (%) (Calc) C	Found (%) (Calc) H	PMR($CDCl_3$) δ ppm
4a	C_6H_5	128-29 (130-32)[25]	70	75	EtOH	94.3 (94.3	5.7 5.7)	—
4b	2-$NO_2C_6H_4$	100-102 (102-103)[15]	78	80	AcOH	81.3 (81.2	4.6 4.6)	—
4c	3-$NO_2C_6H_4$	162-64 (160-62)[15]	65	70	EtOH	81.2 (81.2	4.6 4.6)	6.50-7.95 (*m*, 13H, Ar−*H*), 6.27 (*d*, *J*=15.5 Hz, 1H, −*CH*=C<), 6.42 (*d*, *J*=15.7 Hz, 1H, −*CH*=C<)
4d	4-$NO_2C_6H_4$	220-22 (221-22)[15]	80	90	EtOH	81.3 (81.2	4.6 4.6)	—
4e	4-ClC_6H_4	134-36 (135-37)[17]	75	80	AcOH	83.9 (83.9	4.8 4.8)	—
4f	4-BrC_6H_4	170-72 (172-74)[17]	72	75	EtOH	73.5 (73.5	4.1 4.2)	6.50-8.55 (*m*, 13H, Ar−*H*), 6.27 (*d*, *J*=16.1 Hz, 1H, −*CH*=C<), 6.35 (*d*, *J*=16.2 Hz, 1H, −*CH*=C<).
4g	4-IC_6H_4	140-42 (140-44)[15]	60	65	AcOH	65.3 (65.2	3.7 3.7)	—
4h	2-$CH_3C_6H_4$	112-14 (110-12)[17]	50	58	EtOH	93.9 (93.9	6.1 6.1)	7.40-8.40 (*m*, 13H, Ar−*H*), 6.90 (*d*, *J*=16.4 Hz, 1H, −*CH*=C<), 7.13 (*d*, *J*=16.3 Hz, 1H, −*CH*=C<), 2.38 (*s*, 3H, −CH_3).
4i	4-$CH_3C_6H_4$	150-52 (150-51)[17]	55	60	AcOH	93.8 (93.9	6.1 6.1)	6.70-8.00 (*m*, 15H, Ar−*H*), 2.33 (*s*, 3H, −CH_3)
4j	4-$CH_3OC_6H_4$	175-78 (175-77)[17]	68	75	EtOH	89.1 (89.03	5.8 5.8)	7.20-8.53 (*m*, 13H, Ar−*H*), 6.93 (*d*, *J*=17.0 Hz, 1H, −*CH*=C<), 7.05 (*d*, *J*=16.9 Hz, 1H, −*CH*=C<), 3.87 (*s*, 3H, −OCH_3).
4k	2-$C_{10}H_7$	170-72 (175)[25]	45	50	EtOH	94.5 (94.6	5.4 5.4)	—
4l	1-Br-2-$C_{10}H_6$	165-67 (166-67)[15]	60	65	AcOH	76.2 (76.2	4.1 4.2)	6.90-7.80 (*m*, 15H, Ar−*H*), 6.65 (*d*, *J*=15.9 Hz, 1H, −*CH*=C<), 6.80 (*d*, *J*=16.1 Hz, 1H, −*CH*=C<).

C, 72.5; H, 5.3. $C_{30}H_{26}PBr$ requires C, 72.4; H, 5.2%); IR(KBr): 1450 (νP−C); PMR($CDCl_3$): δ 5.75 (*d*, *J*=15 Hz, 2H, −CH_2−), 7.10-8.40 (*m*, 24H, Ar−*H*).

Reaction of (9-anthrylmethylene)triphenylphosphorane (**2**) *with aromatic aldehydes* (**3a-l**)

Route-A—To a suspension of the ylide **2**, generated from **1** (4 mmol) and sodamide (0.19 g; 5 mmol) in anhyd. benzene (100 ml), was added under nitrogen atmosphere, the aldehyde (**3**; 4 mmol) in benzene (20 ml) and the mixture stirred at room temperature for 4-8 hr, and then refluxed for 5-8 hr. After cooling, the residue containing triphenylphosphine oxide and unreacted sodamide was filtered. The filtrate was concentrated on a steam-bath under reduced pressure and the resulting mass chromatographed over neutral alumina using benzene-pet. ether (1:2) as eluent to give the corresponding *trans*-ethylene (**4**) which was recrystallized from an appropriate solvent (Table 1).

Route-B—To a stirred solution **2**, prepared from **1** (4 mmol) and sodium methoxide (4 mmol) in methanol (100 ml), was added under nitrogen atmosphere, the appropriate aldehyde (**3**; 4 mmol) in methanol (20 ml). The reaction mixture was stirred at room temperature for 6-10 hr and worked up as above. The resulting solid was filtered, washed with methanol twice, dried and purified by column chromatography as described in route-A.

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Synthesis of Phenyl Isoxazoles & Pyrazoles via Cyanoethylation

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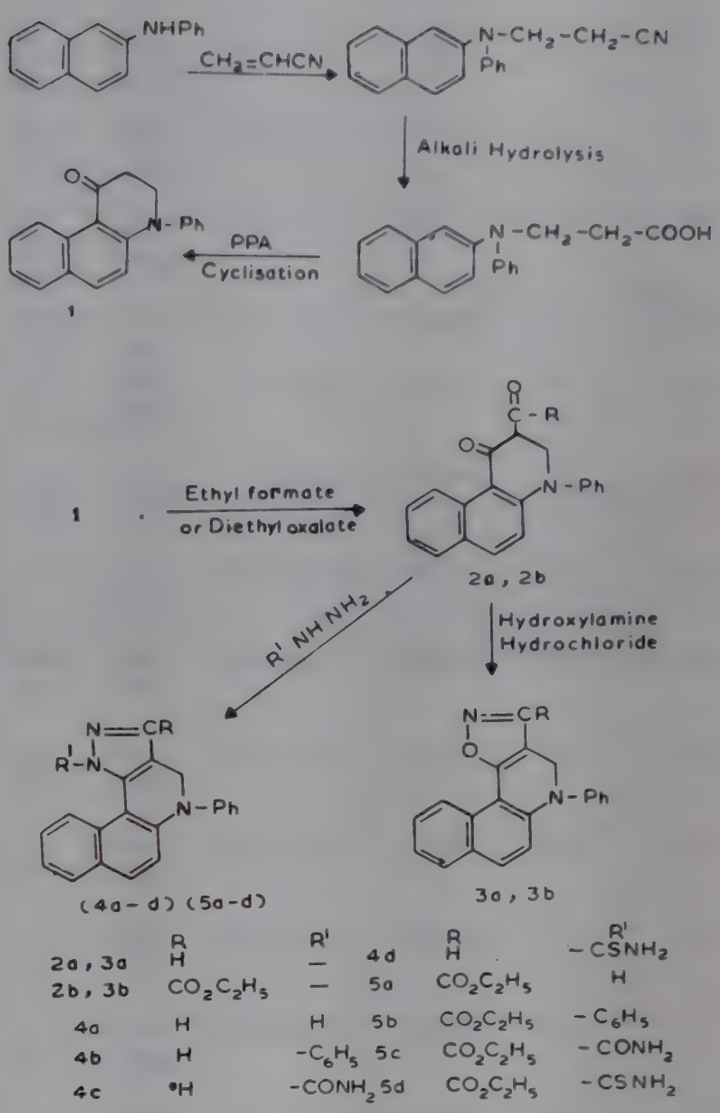
4-Phenyl-1-oxo-1,2,3,4-tetrahydrobenzo[*f*]quinoline (**1**) has been synthesised from N-phenyl-β-naphthylamine via cyanoethylation followed by hydrolysis and cyclisation with polyphosphoric acid, which on treatment with ethyl formate or diethyl oxalate in the presence of sodium ethoxide gives the corresponding 2-acyl derivative (**2a** or **2b**). The latter compounds (**2a**, **2b**) react with hydroxylamine hydrochloride, hydrazine hydrate, phenylhydrazine, semicarbazide hydrochloride and thiosemicarbazide hydrochloride to afford the corresponding isoxazole (**3a**, **3b**) and pyrazole (**4a-d** and **5a-d**) derivatives.

It is reported[1] that cyanoethylated 2-naphthol and naphthalene-2-thiol on treatment with 85% sulphuric acid afford the cyclised products. Some linear benzochromanones have also been synthesised via cyanoethylation followed by cyclisation[2]. The effect of endocrinological activity produced by the fusion of pyrazole or isoxazole ring at 2,3-position of several hormonally active steroids have been studied by Clinton *et al*[3]. Recently[4] many heterocycles containing isoxazole, thiazole, pyrazole or indole moiety fused onto phenanthrene ring at 3,4-position have been synthesised. In our earlier paper[5] we have reported cyanoethylation of 1-naphthol and the synthesis of 4(*H*)-oxo-2,3-dihydronaphtho[1,2-*b*]pyran and its isoxazole and pyrazole derivatives. The synthesis of 1-oxo-4-phenyl-1,2,3,4-tetrahydrobenzo[*f*]quinoline (**1**) via cyanoethylation does not appear to have been reported so far. We therefore wish to report herein the synthesis of **1** and construction of isoxazole and pyrazole moieties on it.

Cyanoethylation of N-phenyl-β-naphthylamine with acrylonitrile in the presence of gl. acetic acid afforded N-(β-naphthyl)-N-phenyl-β-amino-propionitrile (yield 85%) which on alkaline hydrolysis followed by cyclization of the resultant N-(β-naphthyl)-N-phenyl-3-aminopropionic acid (yield 74%) with polyphosphoric acid gave **1** in 60% yield.

Compound **1** when treated with ethyl formate or diethyl oxalate in the presence of sodium ethoxide gave **2a** or **2b**. These 2-acyl derivatives (**2a**,**b**) when treated with hydroxylamine hydrochloride, hydrazine hydrate, phenylhydrazine, semicarbazide hydrochloride and thiosemicarbazide hydrochloride in abs. ethanol afforded 5-phenyl-4,5-dihydrobenzo[5,6]quinolino[3,4-*d*]isoxazole (**3a**), 5-phenyl-4,5-dihydro-1*H*-benzo[5,6]quinolino[4,3-*c*]pyrazole (**4a**), 1,5-diphenyl-4,5-dihydro-1*H*-benzo[5,6]quinolino[4,3-*c*]pyrazole (**4b**), 1-carbamoyl-5-phenyl-4,5-dihydro-1*H*-benzo[5,6]quinolino[4,3-*c*]pyrazole (**4c**), 5-phenyl-1-thiocarbamoyl-4,5-dihydro-1*H*-benzo[5,6]-quinolino[4,3-*c*]pyrazole (**4d**) and 3-carbethoxy-5-phenyl-4,5-dihydrobenzo[5,6]quinolino[3,4-*d*]-isoxazole (**3b**), 3-carbethoxy-5-phenyl-4,5-dihydro-1*H*-benzo[5,6]quinolino[4,3-*c*]pyrazole (**5a**), 3-carbethoxy-1,5-diphenyl-4,5-dihydro-1*H*-benzo[5,6]-quinolino[4,3-*c*]pyrazole (**5b**), 1-carbamoyl-3-carbethoxy-5-phenyl-4,5-dihydro-1*H*-benzo-[5,6]quinolino[4,3-*c*]pyrazole (**5c**) and 3-carbethoxy-1-thiocarbamoyl-5-phenyl-4,5-dihydro-1*H*-benzo-[5,6]quinolino[4,3-*c*]pyrazole (**5d**) respectively. Their structures were established by their elemental analyses and spectral data (Table 1).



	R	R'		R	R'
2a, 3a	H	—	4d	H	$-CSNH_2$
2b, 3b	$CO_2C_2H_5$	—	5a	$CO_2C_2H_5$	H
4a	H	H	5b	$CO_2C_2H_5$	$-C_6H_5$
4b	H	$-C_6H_5$	5c	$CO_2C_2H_5$	$-CONH_2$
4c	H	$-CONH_2$	5d	$CO_2C_2H_5$	$-CSNH_2$

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Table 1—Characterization Data of Various Compounds Prepared

Compd*	Yield	m.p. °C	Mol. formula	Found (%) (Calc.)			PMR($CDCl_3$), δ ppm
				C	H	N	
1	60	178-80	$C_{19}H_{15}NO$	83.3 (83.5	5.6 5.5	5.3 5.1)	6.5-7.4 (11H, *m*, Ar–*H* and $=N-C_6H_5$, 3.8 (2H, *m*, $CH_2-N-C_6H_5$), 2.70 (2H, *t*, CH_2-CO)
2a	55	65-67	$C_{20}H_{15}NO_2$	79.5 (79.7	4.8 5.0	4.4 4.7)	6.4-7.5 (11H, *m*, Ar–*H* and $=N-C_6H_5$), 4.8 (1H, *br*, $HC-CO-H$), 3.9 (2H, *m*, $CH_2-N-C_6H_5$) 9.6 (1H, *br*, $H-C-COH$)
2b	65	48-50	$C_{23}H_{19}NO_4$	73.8 (74.0	5.0 5.1	3.6 3.8)	6.3-7.4 (11H, *m*, Ar–*H* and $=N-C_6H_5$), 4.89 (1H, *s*, $CH-CO$), 4.42 (2H, *g*, $COOCH_3CH_2$), 3.8 (2H, *m*, $CH_2-N-C_6H_5$), 1.43 (3H, *t*, $COOCH_3CH_2$)
3a	57	120-21	$C_{20}H_{14}N_2O$	80.3 (80.5	4.6 4.7	9.4 9.4)	6.5-7.4 (12H, *m*, Ar–*H*, isoxazole-H and $-N-C_6H_5$), 3.8 (2H, *m*, $CH_2-N-C_6H_5$)
4a	63	175-76	$C_{20}H_{15}N_3$	80.8 (80.8	5.3 5.1	14.2 14.1)	12.52 (1H, *br*, *s*, $=N-NH$), 6.5-7.4 (12H, *m*, Ar–*H*, isoxazole-H, and $-N-C_6H_5$), 3.75 (2H, *m*, $CH_2N-C_6H_5$)
4b	47	210-12	$C_{26}H_{19}N_3$	83.6 (83.7	5.3 5.1	11.3 11.3)	7.30 (5H, *s*, $-N-N-C_6H_5$), 6.5-7.42 (12H, *m*, Ar–*H*, isoxazole-H and $CH_2-N-C_6H_5$) 3.70 (2H, *s*, $CH_2-N-C_6H_5$)
4c	42	135-36	$C_{21}H_{16}N_4O$	74.3 (74.1	4.8 4.7	16.7 16.5)	8.52 (2H, *s*, $CONH_2$), 6.5-7.4 (12H, *m*, Ar–*H*, isoxazole-H and $-N-C_6H_5$), 3.9 (2H, *m*, $CH_2-N-C_6H_5$)
4d	46	158-59	$C_{21}H_{16}N_4S$	70.9 (70.8	4.6 4.5	15.8 15.7)	8.82 (2H, *br*, *s*, $CSNH_2$), 6.5-7.4 (12H, *m*, Ar–*H*, isoxazole-H and $-N-C_6H_5$), 3.8 (2H, *m*, $CH_2-N-C_6H_5$)
3b	50	226-27	$C_{23}H_{18}N_2O_3$	74.7 (74.6	5.0 4.9	7.7 7.6)	6.5-7.4 (11H, *m*, Ar–*H* and $-N-C_6H_5$), 4.45 (2H, *q*, $COOCH_3CH_2$), 3.8 (2H, *m*, $CH_2-N-C_6H_5$), 1.43 (3H, *t*, $COOCH_3CH_2$)
5a	60	206-7	$C_{23}H_{19}N_3O_2$	74.9 (74.8	5.3 5.2	11.5 11.4)	12.57 (1H, *br s*, $=N-NH$), 6.5-7.4 (11H, *m*, Ar–*H* and $-N-C_6H_5$), 4.45 (2H, *q*, $COOCH_3CH_2$), 3.9 (2H, *m*, $CH_2-N-C_6H_5$), 1.43 (3H, *t*, $COOCH_3CH_2$)
5b	52	158-59	$C_{29}H_{23}N_3O_2$	78.4 (78.2	5.4 5.2	9.7 9.4)	7.30 (5H, *s*, $=N-N-C_6H_5$), 6.5-7.4 (11H, *m*, Ar–*H* and $CH_2-N-C_6H_5$), 4.45 (2H, *q*, $COOCH_3CH_2$), 3.8 (2H, *m*, $CH_2-N-C_6H_5$), 1.43 (3H, *t*, $COOCH_3CH_2$)
5c	56	170-72	$C_{24}H_{20}N_4O_3$	69.7 (69.9	4.9 4.9	13.8 13.6)	8.62 (2H, *br s*, $CONH_2$), 6.5-7.4 (11H, *m*, Ar–*H* and $-N-C_6H_5$), 4.45 (2H, *q*, $COOCH_3CH_2$), 3.8 (2H, *m*, $CH_2-N-C_6H_5$), 1.43 (3H, *t*, $COOCH_3CH_2$)
5d	60	180-81	$C_{24}H_{20}N_4SO_2$	67.4 (67.3	4.9 4.7	13.2 13.1)	8.82 (2H, *br s*, $CSNH_2$), 6.5-7.5 (11H, *m*, Ar–*H* and $-N-C_6H_5$), 4.45 (2H, *q*, $COOCH_3CH_2$), 3.8 (2H, *m*, $CH_2-N-C_6H_5$), 1.43 (3H, *t*, $COOCH_3CH_2$)

*All the compounds exhibited IR bands characteristic of their structures.

Melting points are uncorrected. PMR spectra were run on a 60 MHz Perkin-Elmer R-32 spectrometer using TMS as internal standard (chemical shifts in δ, ppm) and IR spectra (ν_{max} in cm^{-1}) on a Perkin-Elmer 377 spectrometer. Silica gel was used for TLC and column chromatography.

1-*Oxo*-4-*phenyl*-1,2,3,4-*tetrahydrobenzo*[*f*]-*quinoline*(**1**)

N-(β-Naphthyl)-N-Phenyl-3-aminopropionic acid (10 g) was added to a mixture of phosphorus pentoxide (15 g) and phosphoric acid (8 ml) which was preheated at 100° for 0.5 hr. Heating was continued further for 2 hr with occasional shaking. The mixture was cooled, decomposed with water and extracted with chloroform. The extract was washed successively with sodium bicarbonate solution and water, dried and solvent evaporated to give **1**, yield 5.63 g (60%).

2-*Formyl*-1-*oxo*-4-*phenyl*-1,2,3,4-*tetrahydrobenzo*[*f*]*quinoline* (**2a**)

Freshly distilled ethyl formate (4.4 g; 0.06 mol) was added to an ice-cold suspension of sodium ethoxide (1 g of sodium in 3 ml of dry ethanol) in dry benzene (10 ml) with continuous stirring. To this solution compound **1** (16.38 g; 0.06 mol) in dry benzene (20 ml) was added and the reaction mixture kept in ice-bath for 4 hr with continuous stirring, poured into ice-cold water and extracted with benzene. The extract was dried and solvent removed to give **2a**.

Ethyl 4-*phenyl*-1,2,3,4-*tetrahydrobenzo*[*f*]-*quinolino*-2-*glyoxalate* (**2b**)

To a solution prepared by adding, diethyl oxalate (4.0 g, 0.03 mol) gradually with stirring to a suspension of sodium ethoxide (1.0 g of sodium and 3 ml of super dry ethanol) in dry benzene (15 ml) and warming the mixture for 5 min on a water bath, was added **1** (2.73 g, 0.01 mol) in dry benzene (20 ml) under stirring at room temperature. After the addition was over, the reaction mixture was stirred further for 7 hr at room temperature, poured into water, benzene layer separated and the aqueous layer extracted twice with benzene (100 ml × 2). The combined aqueous layer was acidified with cold dil. hydrochloric acid, extracted twice with ether and the ethereal layer washed successively with 5% sodium bicarbonate solution, water and dried. Removal of solvent and column chromatography of the resulting crude product afforded TLC-pure **2b** which gave violet coloration with ferric chloride.

5-*Phenylbenzoquinoline-isoxazoles* (**3a**, **4a-d**) *and pyrazoles* (**3b**, **5a-d**): *General procedure*

A mixture of **2a** (6.0 g, 0.002 mol) and hydroxylamine hydrochloride, hydrazine hydrate, phenylhydrazine, semicarbazide hydrochloride or thiosemicarbazide hydrochloride (0.002 mol except 0.006 mol hydroxylamine hydrochloride) in gl. acetic acid except ethanol (25 ml) in the case of hydrazine hydrate was heated under reflux for 3 hr, cooled, and poured into water. The precipitate thus obtained was filtered, washed well with water, recrystallized and column chromatographed to give the pure product **3a** or **4**.

In a similar manner **2b** was reacted with various amino derivatives to get the corresponding product **3b** or **5**.

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Synthesis of 4-Aryl-5-arylimino-3-oxo-2-phenyl-1,2,4-thiadiazolidines

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4-Aryl-5-arylimino-3-oxo-2-phenyl-1,2,4-thiadiazolidines(IV) have been prepared by the oxidation of the corresponding 1,3-diaryl-2-S-benzyl-5-phenylisothiobiurets (III) with bromine in chloroform. A plausible mechanism for the reaction has been suggested.

Oxidation of certain substituted 2-S-thiobiurets[1,2] to the corresponding 3-oxothiadiazolidines has been on record. Our interest in the synthesis of heterocyclic systems led us to develop a new and general route for the synthesis of some 4-aryl-4-arylimino-3-oxo-2-phenyl-1,2,4-thiadiazolidines (IV) by oxidative debenzylation of 1,3,5-triaryl-2-S-benzylisothiobiurets (III).

1,3-Diaryl-2-S-benzylisothiocarbamides (IIa-e) were obtained by the benzylation of the corresponding 1,3-diarylthiocarbamides (I). The latter (II) on condensation with phenyl isocyanate afforded the required 1,3-diaryl-2-S-benzyl-5-phenylisothiobiurets (IIIa-e; Table 1). The oxidation of IIIa-e with bromine in chloroform yielded the corresponding 4-aryl-5-arylimino-3-oxo-2-phenyl-1,2,4-thiadiazolidines (IVa-e; Table 1). The structure IV for these compounds was confirmed by their formation from the direct oxidation of the related 1,3-diaryl-5-phenyl-2-thiobiurets (Va-e) with bromine. The latter compounds were obtained by the reductive debenzylation of IIIa-e with dry hydrogen sulphide in pyridine-triethylamine and also from IVa-e under similar reaction conditions (Scheme 1).

The mechanism shown in Scheme 2 appears plausible for the oxidative debenzylation and cyclization of 1,3,5-triaryl-2-S-benzylisothiobiurets (III).

Melting points are uncorrected. IR spectra are recorded in nujol mull on a Perkin-Elmer 720 spectrophotometer.

1,3-*Diaryl*-2-*S*-*benzyl*-5-*phenylisothiobiurets* (*IIIa-e*; *Table* 1)

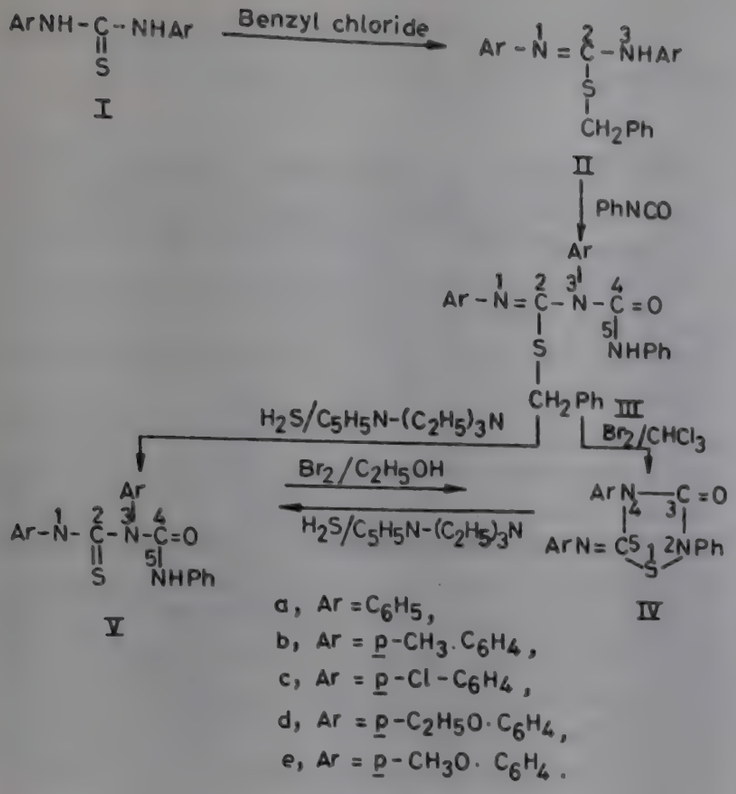
The details of a typical experiment are as follows:

The required, 1,3-di-(*p*-chlorophenyl)thiocarbamide (Ic) was benzylated[3] and a benzene solution of the resultant 1,3-di-(*p*-chlorophenyl)-2-S-benzylisothiocarbamide (IIc) refluxed with phenyl isocyanate (1:1 mol) for 2.5 hr on a water-bath. The reaction was exothermic and a crystalline solid separated out. It was filtered, dried and crystallised from ethanol to give IIIc.

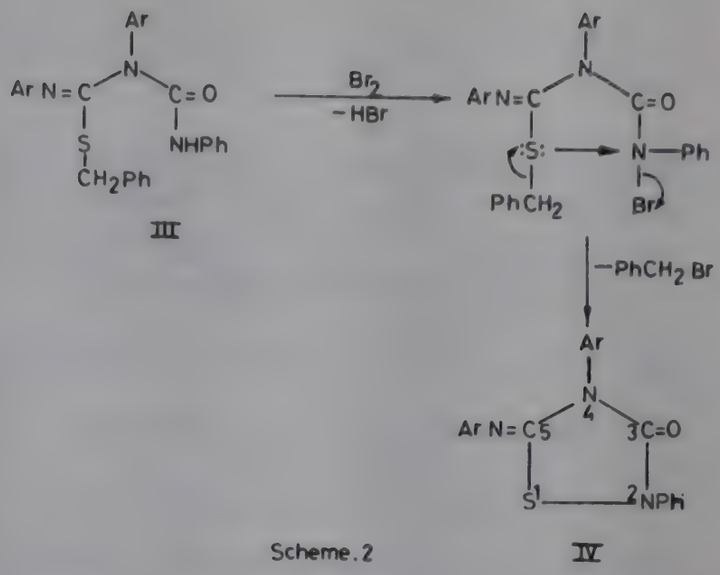
Table 1—Characterisation Data of Compounds III-V

Compd*	Ar	m.p. °C	Yield (%)	Mol. formula	Found (%)		Calc. (%)	
					C	H	C	H
IIIa	C_6H_5	230	70	$C_{27}H_{23}N_3SO$	74.1	5.2	74.1	5.2
IIIb	*p*-CH_3-C_6H_4	202	75	$C_{29}H_{27}N_3SO$	74.6	5.7	74.8	5.8
IIIc	*p*-Cl-C_6H_4	177	68	$C_{27}H_{21}N_3Cl_2SO$	64.0	4.0	64.0	4.1
IIId	*p*-C_2H_5O-C_6H_4	174	62	$C_{31}H_{31}N_3SO_3$	70.7	5.8	70.8	5.9
IIIe	*p*-CH_3O-C_6H_4	101	65	$C_{29}H_{27}N_3SO_3$	70.3	5.4	70.0	5.4
IVa	C_6H_5	290(d)	70	$C_{20}H_{15}N_3SO$	69.4	4.3	69.5	4.3
IVb	*p*-CH_3-C_6H_4	290(d)	75	$C_{22}H_{19}N_3SO$	70.7	5.0	70.7	5.1
IVc	*p*-Cl-C_6H_4	280	76	$C_{20}H_{13}N_3Cl_2SO$	57.8	3.1	57.9	3.1
IVd	*p*-C_2H_5O-C_6H_4	275	62	$C_{24}H_{23}N_3SO_3$	66.4	5.2	66.5	5.3
IVe	*p*-CH_3O-C_6H_4	246	68	$C_{2}H_{19}N_3SO_3$	65.2	4.6	65.2	4.7
Va	C_6H_5	242	68	$C_{20}H_{17}N_3SO$	69.0	4.8	69.2	4.9
Vb	*p*-CH_3-C_6H_4	250	70	$C_{2}H_{21}N_3SO$	70.3	5.4	70.4	5.6
Vc	*p*-Cl-C_6H_4	230	72	$C_{20}H_{15}N_3Cl_2SO$	57.6	3.5	57.7	3.6
Vd	*p*-C_2H_5O-C_6H_4	140	58	$C_{24}H_{25}N_3SO_3$	66.1	5.7	66.2	5.7
Ve	*p*-CH_3O-C_6H_4	180	62	$C_{2}H_{21}N_3SO_3$	64.8	5.1	64.9	5.2

*IR (IIIa-e): 1650-1720(C=O), 1540-1560(C=N), 3300-3310 cm^{-1} (NH); IR (IVa-e): 1650-1700(C=O), 1560-1625 cm^{-1} (C=N); IR (Va-e): 1640-1710(C=O), 1240-1300 (C=S), 3300-3320 cm^{-1} (NH).



Scheme.1



Scheme.2

4-*Aryl*-5-*arylimino*-3-*oxo*-2-*phenyl*-1,2,4-*thiadiazolidines* (*IVa-e*)

(*i*) *By oxidative debenzylation of* 1,3-*diaryl*-2-*S*-*benzyl*-5-*phenylisothiobiurets with bromine in chloroform*

To a warm solution of IIIc (3 g) in chloroform (8 ml) was added bromine with brisk stirring until the colour of bromine persisted. Evolution of benzyl bromide was evident by its lachrymatory fumes. To complete the reaction the mixture was allowed to stand for 30 min. The semisolid product was washed with ether and a little ethanol added to it to afford IVc which was crystallised from ethanol.

(*ii*) *By oxidation of* 1,3-*diaryl*-5-*phenyl*-2-*thiobiurets* (*Va-e*) *with bromine in dilute ethanol*

The thiobiurets Va-e (Table 1) were oxidised with bromine in ethanolic solution and ether added to the reaction mixture to precipitate the corresponding 1,2,4-thiadiazolidines (IV) which were found to be identical with those prepared from III (*vide supra*).

1,3-*Diaryl*-5-*phenyl*-2-*thiobiurets* (*Va-e*; *Table* 1)

(*i*) *By reductive debenzylation of IIIa-e*

2-S-Benzylisothiobiurets (III) were reduced by passing hydrogen sulphide (for 6 hr) in pyridine-triethylamine (6:1) medium[4]. The reaction mixture on pouring over crushed ice and acidification with hydrochloric acid afforded the related 2-thiobiurets (V) which were filtered and crystallised from ethanol.

(*ii*) *By reduction of IV*

Thiadiazolidines (IVa-e) were reduced in a mixture of pyridine-triethylamine by passing hydrogen sulphide for about 5 hr. On cooling and acidification of the reaction mixture with dil. HCl, the expected 2-thiobiurets (V) were obtained, which were crystallised from ethanol. These products were found to be identical (m.m.p.) with those obtained by reductive debenzylation of 2-S-benzylisothiobiurets (III; *vide supra*).

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Synthesis of Acylamino Acids & Acylamino Acid Amides by Simultaneous Reduction & Hydrolysis of Unsaturated 2,4-Disubstituted 2-Imidazolin-5-ones

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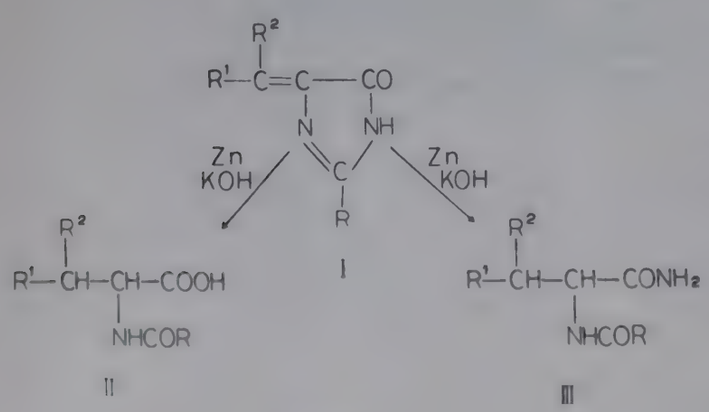
Twelve acylamino acids (II) and two acylamino acid amides (III) have been prepared by the simultaneous reduction and hydrolysis of unsaturated 2, 4-disubstituted 2-imidazolin-5-ones (I) with a mixture of zinc dust and potassium hydroxide solution.

The simultaneous reduction and hydrolysis of unsaturated 2, 4-disubstituted 2-imidazolin-5-ones (I) to acylamino acids (II) with a mixture of zinc dust and potassium hydroxide solution[1] is superior to the other two existing methods[2,3] for the conversion of I into II. However, this method was employed[1] for the synthesis of only five compounds of the type II which are largely used for the resolution of amino acids[4] and for the synthesis of peptides[5]. The present note describes such an improved method which has been employed for the synthesis of a number of acylamino acids (II) and two acylamino acid amides (III) (see Scheme 1).

We carried out several experiments by changing the reaction conditions to improve the yields of II but the attempts were not very successful. However, the method of isolation of II from the reaction mixture could be improved to a large extent. The original method[1] of isolation was time consuming, expensive and gave the crude product (II) much impure in some cases. In the present work, after removing the unreacted zinc dust, the solution containing II was readily purified by completely precipitating the impurities with a calculated amount of gl. acetic acid. Compound II which separated from the solution on acidification with hydrochloric acid was almost pure in every case. The reproducibility of yields of II was established by repeating the preparation of N-benzoyl-β-phenylalanine (IIa: $R = R^1 = C_6H_5$; $R^2 = H$) thrice by taking 2 g, 4 g and 8 g of 2-phenyl-4-benzylidene-2-imidazolin-5-one (Ia: $R = R^1 = C_6H_5$; $R^2 = H$). In the case of 2-phenyl-4-cyclopentylidene- and 2-phenyl-4-cyclohexylidene-2-imidazolin-5-ones (If and Im), the corresponding acylamino acid amides (III) separated during the reaction and were isolated from the unreacted zinc dust. However, in the first case (If) some IIf was also obtained. Pure zinc dust must be used for the reaction. Both potassium and sodium hydroxide solutions are suitable for the reaction but the former gives better yields of II and III.



Scheme 1

During reduction and hydrolysis of I the exocyclic double bond may be first reduced and the saturated 2-imidazolin-5-ones thus produced may undergo hydrolysis to III and then to II. The yields of II given in Table 1 indicate that the substituents in the 2-position of I affect the yields very much compared to those in the 4-position. As expected the acylamino acids (II) and acylamino acid amides (III) prepared were found to be optically inactive and therefore they are racemic mixtures.

The imidic acid ester-glycine ester method[2,3,7] was employed for the synthesis of I required for the preparation of II and III because it is superior to the other existing methods[1-3,6-11].

Imidic acid methyl ester hydrochlorides

The methyl ester hydrochlorides of benzimidic acid (m.p. 98-99°), *p*-toluimidic acid (m.p. 164-65°) and phenylacetimidic acid (m.p. 74-75°) were prepared in 96, 98 and 86% yields respectively according to the directions of Dox[12] and Kidwai and Devasia[2], but in the last case dry ether was added when the product began to separate and then placed in a refrigerator. Being not very stable at room temperature the imidic acid ester hydrochlorides were stored in a refrigerator.

Unsaturated 2,4-disubstituted 2-imidazolin-5-ones (I)

Compounds I, except If and Im (R_1R_2 = cyclohexylidene; $R = C_6H_5$), were prepared according to method-B[2] of the imidic acid ester-glycine ester method by heating a mixture of the aldehyde (0.02 mol), the imidic acid methyl ester hydrochloride (0.024 mol) and glycine ethyl ester hydrochloride (0.03 mol) in the

Table 1—Physical Data of Unsaturated 2,4-Disubstituted 2-Imidazolin-5-ones (I) and Acylamino Acids (II)

Compd	R^1, R^2	2-Imidazolin-5-ones (I)				Acylamino acids (II)			
		Yield (%)	m.p.* °C	N (%) Found	N (%) Calc.	Yield (%)	m.p. °C	N (%) Found	N (%) Calc.
				R = Phenyl					
a	Phenyl, H	70	284-85 (284-85)[11]	11.4	11.3	67	188-89 (188-89)[3]	5.0	5.2
b	*p*-Methoxyphenyl, H	69	302-3 (302-3)[11]	10.2	10.1	60	178-79 (176.5-77.5)[2]	4.5	4.7
c	3,4-Dimethoxyphenyl, H	76	269-70 (269-70)[11]	9.0	9.1	60	185-86 (180-81)[13]	4.3	4.3
d	3,4-Methylenedioxyphenyl, H	78	303-5 (296-97)[11]	9.7	9.6	50	190-91 (171-72)[14]	4.7	4.5
e	*o*-Chlorophenyl, H	63	268-69 (268-69)[11]	9.6	9.9	44	190-91 (189-90)[3]	4.4	4.6
f	$-(CH)_4-$	62	222-23 (222-23)[3]	12.0	12.4	22	194-95 (110-11)[14]	6.0	5.7
				R = *p*-Tolyl					
g	Phenyl, H	77	304-5 (304-5)[11]	11.2	10.7	33	196-97 (196-97)[3]	5.1	4.9
h	*p*-Methoxyphenyl, H	78	269-70 (269-70)[11]	9.3	9.6	27	179-80†	4.6	4.5
i	3,4-Dimethoxyphenyl, H	75	262-63†	8.4	8.7	43	213-14†	3.7	4.1
j	3,4-Methylenedioxyphenyl, H	89	328-29†	8.7	9.2	19	200-201†	3.8	4.3
				R = Benzyl					
k	*p*-Methoxyphenyl, H	48	191-93 (186-87)[2]	9.8	9.6	24	152-54 (154-55)[2]	4.3	4.5
l	3,4-Methylenedioxyphenyl, H	43	216-17†	9.3	9.2	24	167-68†	4.3	4.3

*Solvents used for crystallisation were: 2-methylpropan-1-ol for Ia, Ib, Ic, Id, Ie, Ig, Ih, Ii, Ij; ethanol for Ik, Il; benzene for If.
†Compounds reported for the first time.

presence of sodium hydrogencarbonate (0.057 mol) and benzene (10 ml) around 72° for 1 hr. However, in the case of I where $R = C_6H_5CH_2$, the product was washed with hot benzene, water and ether. The compounds were crystallised from an appropriate solvent (Table 1).

Compounds If and Im were prepared as described earlier[3] by the method of Lehr and coworkers[7].

Acylamino acids (II; Table 1)

A mixture of crude I (2 g) and pure zinc dust (5 g) was refluxed with 10% potassium hydroxide solution (70 ml) for 1 hr. The flask was shaken often until I dissolved to form a yellow solution and then occasionally. There was a copious evolution of ammonia due to the reduction and hydrolysis of I to II and the solution gradually became colourless. The reaction mixture was allowed to cool, filtered through a sintered glass funnel to remove the unreacted zinc dust and the colourless filtrate treated with gl. acetic acid (8.5 ml) when the impurities precipitated out as a pale yellow solid. The mixture was cooled in ice-cold water and filtered to remove the impurities. The perfectly colourless filtrate was acidified with conc. hydrochloric acid (14 ml), when II separated out as colourless crystals. After cooling in a refrigerator overnight the crystals were filtered, washed with water and ether and recrystallised from 50% ethanol.

N-Benzoyl-α-cyclopentylglycine amide
[IIIa: $R = C_6H_5$; $R^1R^2 = (CH_2)_4$]

A mixture of 2-phenyl-4-cyclopentylidene-2-imidazolin-5-one (2 g) [If: $R = C_6H_5$; $R^1R^2 = (CH_2)_4$] and pure zinc dust (5 g) was refluxed with 14% potassium hydroxide solution (50 ml). The flask was shaken often until the 2-imidazolin-5-one dissolved and then occasionally. Within 10 min of refluxing the amide began to separate out as colourless crystals. After a total refluxing period of 1 hr the flask was allowed to cool and the amide containing the unreacted zinc dust filtered on a sintered glass funnel and washed with water. The mixture of amide and zinc

dust was boiled with ethanol (75 ml) to dissolve the amide, filtered, concentrated to 35 ml and allowed to cool. The colourless crystals of amide (m.p. 239-40°) thus separated were collected (0.52 g). A second crop (0.16 g) of the amide was obtained from the mother liquor on further concentration. Thus, the total yield of IIIa was 0.68 g (31%). On recrystallisation from ethanol the amide melted at 248-49° (lit.[3], m.p. 248-49°). The m.m.p. with an authentic sample showed no depression (Found: N, 11.2. Calc. for $C_{14}H_{18}N_2O_2$: N, 11.4%).

By the method described under acylamino acids (II), N-benzoyl-α-cyclopentylglycine (IIf) was also isolated in 22% yield from the solution obtained on filtering the precipitated amide IIIa containing the unreacted zinc dust.

N-Benzoyl-α-cyclohexylglycine amide
[IIIb: $R = C_6H_5$; $R^1R^2 = (CH_2)_5$]

It was prepared in a similar way as described above. The mixture of amide and zinc dust was boiled with ethanol (200 ml) to dissolve the amide, filtered, concentrated to 100 ml and cooled. The colourless crystals of the amide (m.p. 276-77°) thus separated were collected (1.2 g). A second crop (0.12 g) of the amide was obtained from the mother liquor on further concentration. Thus, the total yield of IIIb was 1.32 g (63%). Recrystallisation of IIIb from ethanol did not raise its m.p. (lit.[3], m.p. 276-77°). The m.m.p. with an authentic sample showed no depression (Found: N, 11.3. Calc. for $C_{15}H_{20}N_2O_2$: N, 10.8%).

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Synthesis & Some Reactions of 2-(α/β-Naphthyl)-3,1-benzoxazin-4(*H*)-ones & 3-Amino-2-(β-naphthyl)quinazolin-4(3*H*)-one

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2-(α/β-Naphthyl)-3,1-benzoxazin-4(*H*)-ones (I) have been prepared by the reaction of α- or β-naphthoyl chloride (2 mol) and anthranilic acid (1 mol) in the presence of a catalytic amount of pyridine, and their reactions with amines, formamide and active methylene compounds have been studied. 3-aminoquinazolinone (X) has been synthesized by the action of hydrazine hydrate on Ib in *n*-butanol and its reaction with acetic anhydride, aldehydes, esters, and P_2S_5 has been investigated. Cleavage of the C=S bond in the thione XIV with hydrazine hydrate and copper bronze has been observed.

In continuation of our study on 2-substituted 3,1-benzoxazin-4(*H*)-ones and 4-quinazolinones[1-6], we report herein the reaction of anthranilic acid (1 mol) in pyridine with naphthoyl chlorides (2 mol) as a preparative method for the preparation of 2-(α/β-naphthyl)-3,1-benzoxazin-4(*H*)-ones (I). On the other hand, treatment of anthranilic acid with equimolar amounts of naphthoyl chlorides in the presence of a catalytic amount of pyridine yielded N-(α/β-naphthoyl)anthranilic acids (II) which on heating with acetic anhydride yielded I[7]. Acid hydrolysis of I gave II.

It was previously stated[2,7] that primary amines react with 2-substituted-3,1-benzoxazin-4(*H*)-ones in the presence of anhyd. zinc chloride to give 2,3-disubstituted-4-quinazolones. In the present study aminolysis of Ib with primary aromatic amines such as *p*-anisidine and/or *m*-anisidine in boiling ethanol gave the corresponding N(β-naphthoyl)anthranilic acid anilides (IIIa and IIIb). Similarly, the secondary amine piperidine reacted with Ia to give N-(α-naphthoyl)-anthranilic acid piperidide (IV).

N-(β-Naphthoyl)anthranilic acid (IIb) on treatment with formamide underwent ring closure affording 2-(β-naphthyl)-4-quinazolinone (V) which exists in the lactam⇌lactim tautomeric equilibrium (VA⇌VB) (Scheme 1).

We have studied earlier[1] the action of active methylene compounds on 3,1-benzoxazin-4(*H*)-ones. In this investigation, we have found that 2-(β-naphthyl)-3,1-benzoxazin-4(*H*)-one (Ib) reacts in a similar manner with ethyl acetoacetate, diethyl malonate and ethyl cyanoacetate in refluxing pyridine to give one and the same product ethyl *o*-(β-naphthamido)benzoylacetate (VII) and this led us to conclude that the reaction takes place via the opening of the heterocyclic ring in Ib by the carbanions derived from the active methylene compounds to give the intermediate VI (R=CH_3CO, $CO_2C_2H_5$ or CN) (Scheme 2). The β-ketoester (VII) undergoes acid hydrolysis with ethanolic KOH to give N-(β-naphthoyl)anthranilic acid (IIb).

The reaction of VII with hydrazine hydrate and phenylhydrazine afforded the pyrazolinone derivatives (VIIIa and VIIIb). On the other hand, treatment of N-(β-naphthoyl)anthranilic acid (IIa) with 3-methyl-1-phenyl-2-pyrazolin-5-one afforded 4 [N-(α-naphthoyl)-*o*-aminobenzoyl]-2-pyrazolin-5-one (IX) (Scheme 1).

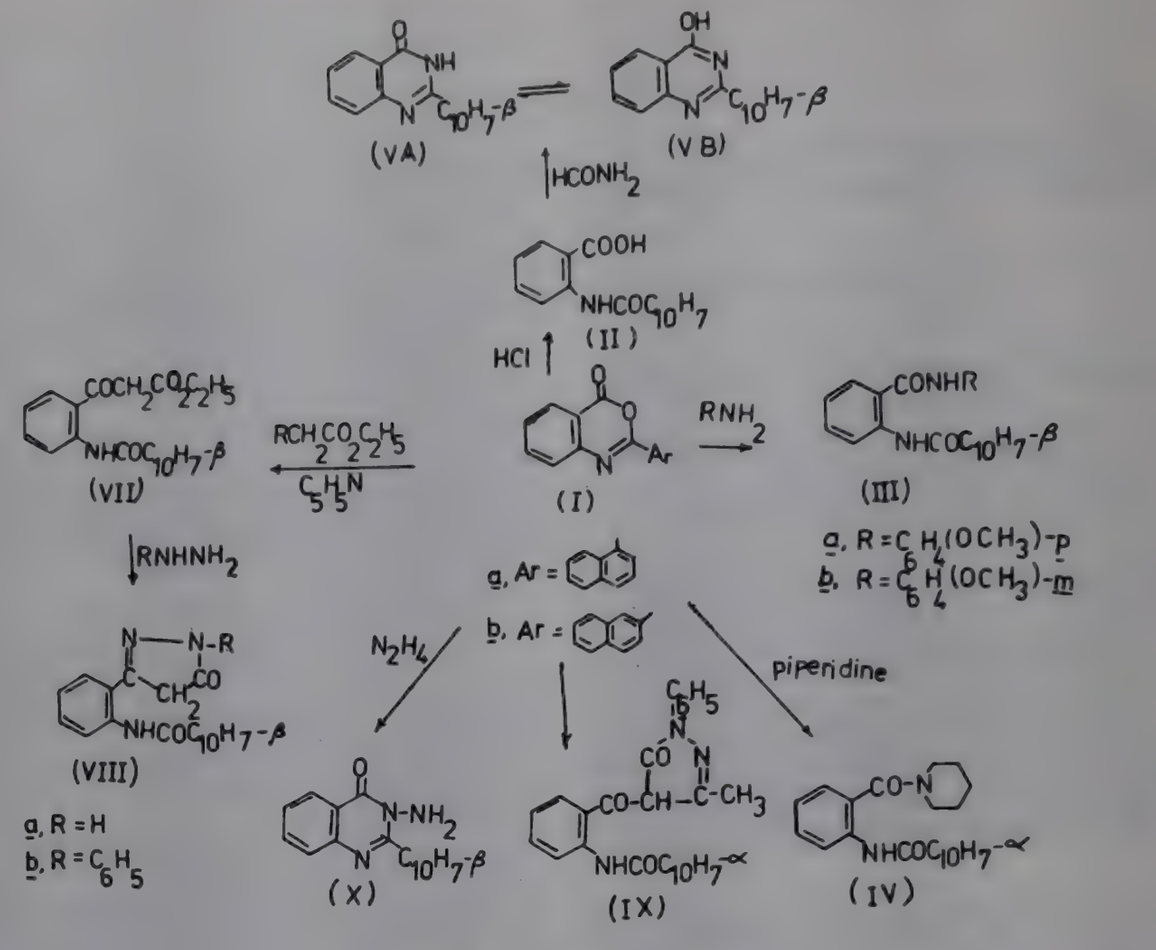
Hydrazinolysis of Ib with hydrazine hydrate in refluxing *n*-butanol gave 3-amino-2-(β-naphthyl)quinazolin-4-(3*H*)-one (X). Acetylation of X with acetic anhydride afforded 3-acetylamino-2-(β-naphthyl)-quinazolin-4(3*H*)-one (XI). Condensation of X with aromatic aldehydes such as *p*-chlorobenzaldehyde, *p*-methoxybenzaldehyde and *p*-N,N-dimethylamino-benzaldehyde in the presence of piperidine in refluxing ethanol gave the corresponding schiff bases (XIIa-c). The compound X also underwent condensation with esters, namely ethyl chloroformate, ethyl chloroacetate and/or ethyl acetoacetate in boiling *n*-butanol to give XIIIa-c (Scheme 3). The reaction of X with P_2S_5 in dry xylene gave the thione XIV which on treatment with hydrazine hydrate underwent cleavage of the C=S to give the hydrazone derivative (XV)[6] whereas on heating with copper bronze in dry xylene it gave the coupling product 2,2′-di(β-naphthyl-$\Delta^{4,4'}$-bi-3,1-benzoquinazoline (XVI)[4].

The presence of bulky naphthyl group in position-2 decreased the yield of the products in the above reactions and this is due to the steric hindrance as reported by other investigators[8].

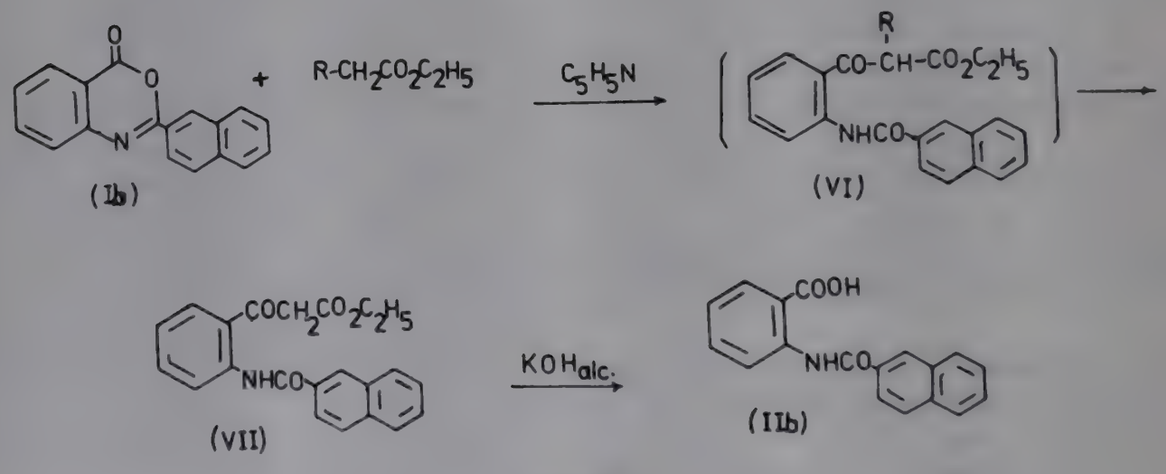
IR spectra were recorded in KBr on a Beckman infrared spectrophotometer (ν_{max} in cm^{-1}) and PMR spectra on a Varian instrument using TMS as internal standard (chemical shifts in δ, ppm). All melting points are uncorrected. Characterization data of all the compounds prepared are given in Table 1.

2-(α/β-Naphthyl)-3,1-benzoxazin-(4H)-ones (Ia and Ib):

A solution of anthranilic acid (0.01 mol) in pyridine (30 ml) was added to α- or β-naphthoyl chloride



SCHEME 1



SCHEME 2

(0.02 mol). The solution was shaken for 15 min, left aside at room temperature for further 30 min with occasional shaking, stirred in cold water, and the solid separated filtered off, washed with water and crystallized from a proper solvent to give Ia or Ib.

N-(α/β-Naphthoyl)anthranilic acids (II)

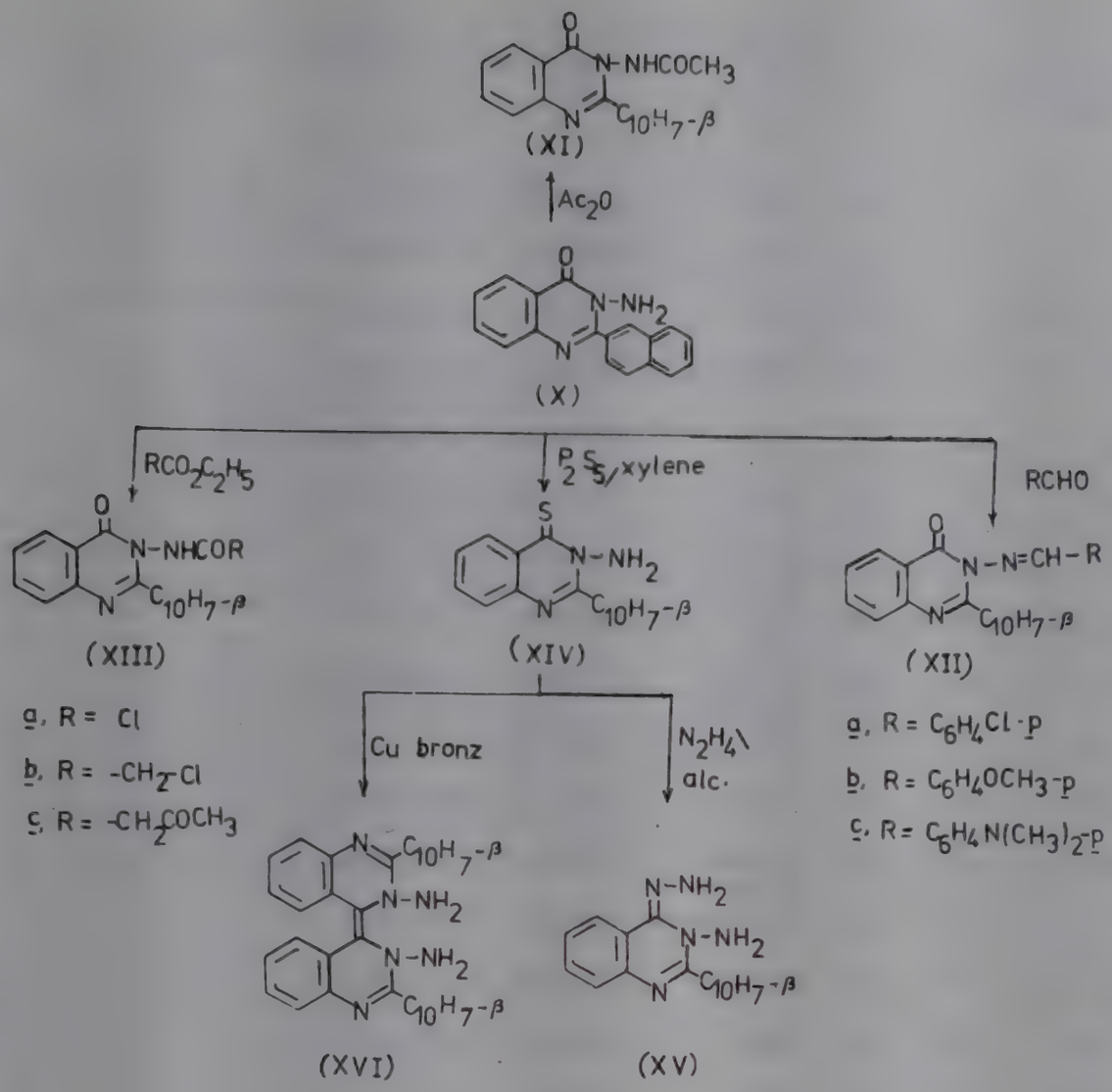
(a) A solution of anthranilic acid (0.01 mol) in pyridine (20 ml) was treated with α- or β-naphthoyl chloride (0.01 mol). The solution was shaken for 15 min, stirred in cold water, and the separated solid crystallized from a suitable solvent to give IIa or IIb.

(b) A suspension of I (0.01 mol) in water (100 ml) was acidified with a few drops of HCl and heated under reflux for 30 min. The separated product was recrystallized from a suitable solvent to give II.

A mixture of II (0.01 mol) and Ac_2O (20 ml) was refluxed for 1 hr, and the resultant solution left to evaporate slowly in a porcelain dish. The precipitated product was found to be identical with I obtained by the action of α- or β-naphthoyl chloride on anthranilic acid.

Action of amines on Ib: Formation of IIIa and IIIb

A solution of Ib (0.01 mol) and *p*-anisidine or *m*-



SCHEME 3

anisidine (0.01 mol) in ethanol was heated under reflux for 5 hr. The product that separated on cooling was crystallized from a suitable solvent to give IIIa or IIIb; IR: 1650-1680 (C=O) and 3200-3300 (NH).

N-(α-Naphthoyl)anthranilic acid piperidide (IV)

A solution of Ia (0.01 mol) and piperidine (0.01 mol) in ethanol (30 ml) was heated under reflux for 3 hr, cooled and the separated product crystallized from pet. ether (b.p. 100-120°) to give IV; IR: 1660, 1680 (amide-I and amide-II) and 3200 (NH).

2-(β-Naphthyl)-4-quinazolinone (V)

A mixture of IIb (0.01 mol) and formamide (0.015 mol) was heated at 196° for 3 hr. The resultant product was washed with water and crystallized from xylene to give V; IR: 3500-3400 (OH), 3200, 1680 (C=O of cyclic lactam) and 1620 (C=N).

Ethyl o-(β-naphthamido)benzoylacetate (VII)

A mixture of Ib (0.01 mol) and ethyl acetoacetate, diethyl malonate or ethyl cyanoacetate (0.03 mol) in dry pyridine (50 ml) was heated under reflux for 24 hr, poured onto ice-cold HCl, and the precipitated product filtered and crystallized from light petrol (b.p. 100-120°) to give VII; IR: 1720 (ester C=O), 1680 (CONH) and 3200 (NH).

The compound VII (0.01 mol) on hydrolysis with ethanolic KOH (20 ml; 10%) under reflux for 2 hr followed by usual work-up gave IIb, m.p. and m.m.p. 196°.

Pyrazolinone derivatives (VIIIa,b)

A solution of VII (0.01 mol) and hydrazine hydrate or phenylhydrazine (0.01 mol) in *n*-butanol (50 ml) was heated under reflux for 3 hr, cooled and the separated solid crystallized from a suitable solvent to give VIIIa or VIIIb; IR: 1640 (C=N), 1700-1720 (C=O), 1600 (C=C) and 3200 (NH).

4-[N-(α-Naphthoyl)-o-aminobenzoyl]-2-pyrazolin-5-one (IX)

A mixture of Ia (0.01 mol) and 3-methyl-1-phenyl-2-pyrazolin-5-one (0.03 mol) in dry pyridine (50 ml) was

Table 1—Characterization Data of Various Compounds Prepared

Compd	Yield (%)	m.p. °C	Crystallized from	Colour	Mol. formula	Found %) (Calc.)		
						C	H	N
Ia	32	105	Ac_2O	Colourless	$C_{18}H_{11}NO_2$	79.2 (79.1	4.0 4.0	5.3 5.1)
Ib	48	112	Ac_2O	Colourless	$C_{18}H_{11}NO_2$	79.3 (79.1	4.1 4.0	5.2 5.1)
IIa	76	159	C_6H_6	Colourless	$C_{18}H_{13}NO_3$	74.4 (74.2	4.5 4.5	5.0 4.8)
IIb	85	196	EtOH-C_6H_6	Colourless	$C_{18}H_{13}NO_3$	73.9 (74.2	4.6 4.5	4.9 4.8)
IIIa	72	195	EtOH	Colourless	$C_{25}H_{20}N_2O_3$	75.9 (75.8	5.1 5.1	7.2 7.1)
IIIb	74	180	EtOH	Pale brown	$C_{25}H_{20}N_2O_3$	75.8 (75.8	5.3 5.1	7.1 7.1)
IV	63	153	Pet. ether (100-120°)	Colourless	$C_{23}H_{22}N_2O_2$	77.2 (77.1	6.3 6.1	8.0 7.8)
V	81	212	Xylene	Colourless	$C_{18}H_{12}N_2O$	79.5 (79.4	4.6 4.4	10.3 10.3)
VII	72	115	Pet. ether (100-120°)	Colourless	$C_{22}H_{19}NO_4$	73.2 (73.1	5.4 5.3	4.0 3.9)
VIIIa	68	180	C_6H_6-Toluene	Colourless	$C_{20}H_{15}N_3O_2$	73.2 (72.9	4.4 4.6	12.9 12.8)
VIIIb	86	210	Toluene	Buff	$C_{26}H_{19}N_3O_2$	77.1 (77.0	4.8 4.7	10.5 10.4)
IX	64	155	Pet. ether (80-100°)	Yellowish	$C_{28}H_{21}N_3O_3$	75.3 (75.2	4.9 4.7	9.5 9.4)
X	85	208	EtOH-Toluene	Yellowish	$C_{18}H_{13}N_3O$	75.1 (75.3	4.4 4.5	14.7 14.6)
XI	78	158	dil.AcOH	Colourless	$C_{20}H_{15}N_3O_2$	73.0 (72.9	4.6 4.6	13.0 12.8)
XIIa	88	197	EtOH	Colourless	$C_{25}H_{16}N_3OCl$	73.3 (73.3	4.1 3.9	10.4 10.3)
XIIb	85	185	EtOH	Yellowish	$C_{26}H_{19}N_3O_2$	77.3 (77.0	4.8 4.7	10.5 10.4)
XIIc	74	227	Toluene	Yellow	$C_{27}H_{22}N_4O$	77.8 (77.5	5.4 5.3	13.5 13.4)
XIIIa	65	125	C_6H_6	Colourless	$C_{19}H_{12}N_3O_2Cl$	65.3 (65.2	3.5 3.4	12.2 12.0)
XIIIb	75	202	AcOH	Colourless	$C_{20}H_{14}N_3O_2Cl$	66.2 (66.0	4.0 3.9	11.8 11.6)
XIIIc	47	187	Toluene	Brownish	$C_{22}H_{17}N_3O_3$	71.3 (71.2	4.8 4.6	11.5 11.3)
XIV	60	156	Xylene	Yellow	$C_{18}H_{13}N_3S$	71.4 (71.3	4.4 4.3	14.1 13.9)
XV	61	128	Pet. ether (100-120°)	Colourless	$C_{18}H_{15}N_5$	72.0 (71.8	5.1 5.0	23.5 23.3)
XVI	55	193	Xylene	Colourless	$C_{36}H_{26}N_6$	79.9 (79.7	5.0 4.8	15.6 15.5)

heated under reflux for 24 hr, poured onto cold dil. HCl and the separated solid crystallized from light petrol (b.p. 80-100°) to give IX; IR: 1640 (C = N), 1680 (C = O) and 1670 (CONH).

3-*Amino*-2-(*β-naphthyl*)*quinazolin*-4-(3*H*)-*one* (*X*)

A solution of Ib (0.01 mol) and hydrazine hydrate (0.01 mol) in ethanol (50 ml) was heated under reflux for 3 hr, cooled and the separated solid crystallized from EtOH-toluene to give X; IR: 1650 (C = N), 1670 (C = O) and 3300 (NH); PMR ($CDCl_3$): 7.3 (*m*, 7H, $C_{10}H_7$), 7.8 (*m*, 4H, C_6H_4-) and 5.15 (*s*, 2H, NH_2).

3-*Acetylamino derivative* (*XI*)

Compound X (0.01 mol) was refluxed with an excess of acetic anhydride for 6 hr, and the reaction mixture left to evaporate slowly in a porcelain dish. After evaporation of the excess acetic anhydride, a solid separated out which on crystallization from dil. acetic acid gave XI; IR: 1680 ($COCH_3$), 3210 (NH), 1650 (CONH) and 1630 (C = N).

Condensation of X with *p*-chlorobenzaldehyde, *p*-methoxybenzaldehyde and/or *p*-N,N-dimethylaminobenzaldehyde in ethanol (50 ml) with a few drops of piperidine was carried out under reflux for 4hr. The reaction mixture was cooled and the separated solid crystallized from suitable solvent to give XII; IR: 1670 (C=O) and 1650 (C=N) (*v*NH was absent).

3-Carboxamido-2-(β-naphthyl)quinazolin-4(3H)-ones (XIIIa-c)

A mixture of X (0.01 mol) and ethyl chloroformate, ethyl chloroacetate or ethyl acetoacetate (0.03 mol) in *n*-butanol (50 ml) was heated under reflux for 24 hr and excess *n*-butanol removed under reduced pressure. The resulting solid on crystallization from an appropriate solvent gave XIII; IR: 1650-1670 (C=O), 1650-1680 (CONH), 3230-3400 (NH) and 1750 (COCl in the case of XIIIa).

Action of P_2S_5 on X: Formation of the thione XIV

A solution of X (0.01 mol) and P_2S_5 (0.02 mol) in dry xylene (100 ml) was heated under reflux for 6 hr, filtered while hot, concentrated, cooled and the separated solid crystallized from xylene to give XIV; IR: 1330 (C=S), 1625 (C=N) and 3320 (NH).

A solution of XIV (0.01 mol) and hydrazine hydrate (0.03 mol) in ethanol (50 ml) was refluxed for 5 hr, cooled and the separated solid crystallized from light petrol (b.p. 100-120°) to give XV.

A mixture of XIV (0.01 mol) and copper bronze (0.005 mol) in dry xylene (20 ml) was heated for 4 hr, filtered while hot to make free from copper bronze, cooled and the separated solid crystallized from xylene to give the coupling product XVI; IR (XV and XVI): 3200-3300 (NH), 1610-1630 (C=N) and 1610 (C=C).

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Reactivity of 2-Hydroxy-2′-nitroacetophenones: Part II†—Synthesis of 2-(3′-Chromonyl)-3-nitrochromanones & Their Conversion into Chromones

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Chromone-3-carboxaldehydes (II) undergo condensation with 2-hydroxy-2′-nitroacetophenones (I) to give compounds whose structures have been established as III from spectral data. Compounds III are brominated to IV which on dehydrobromination give the corresponding chromones (Va-d). All these compounds have been screened for their antimicrobial activity.

It has been reported from our laboratories that the cyclocondensation of 2-hydroxy-2′-nitroacetophenones (I) with aromatic aldehydes in the presence of ammonium acetate in gl. acetic acid gives 3-nitro-2-phenylchromanones[1]. In continuation of this work we now report the synthesis of 2-(3′-chromonyl)-3-nitrochromanones by condensing I with chromone-3-carboxaldehydes (II). We were prompted to take up the present investigation because bichromones, bischromones, disodium cromoglycate and compounds containing a carbonyl group adjacent to a nitro group exhibit anti-anaphylactic activity[2-11].

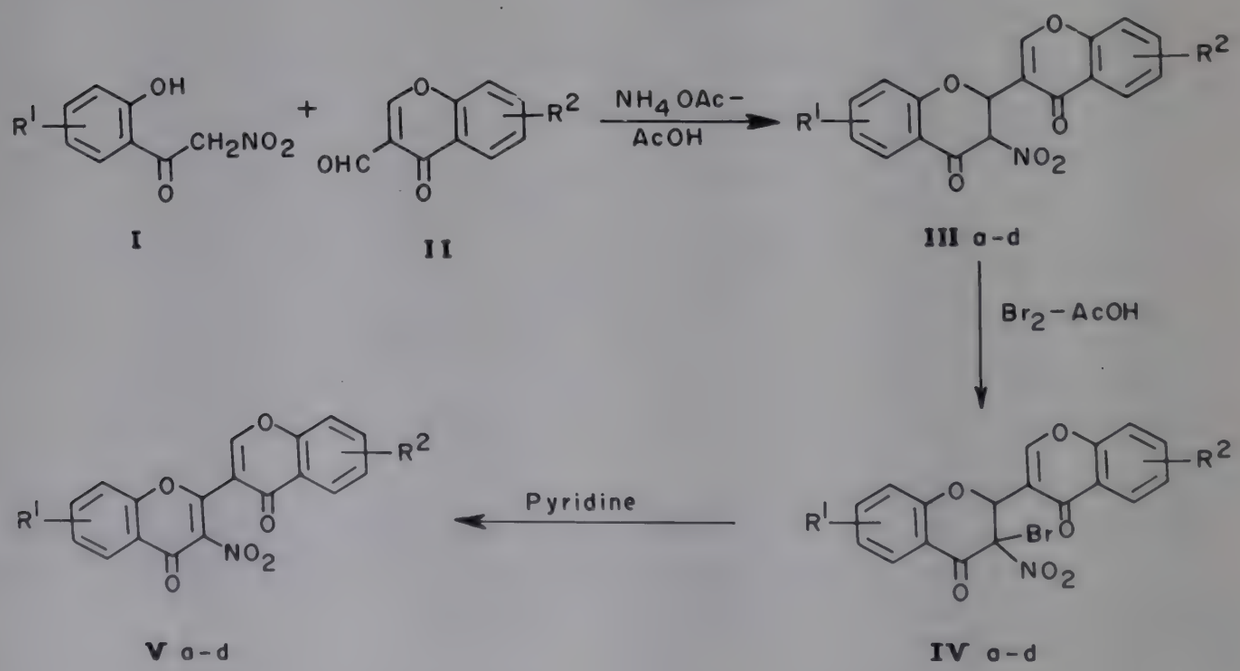
The cyclocondensation of I with II in the presence of ammonium acetate in gl. acetic acid resulted in compounds whose structures were established as 2-(3′-chromonyl)-3-nitrochromanones (IIIa-d) on the basis of spectral and analytical data (Table 1). These compounds (IIIa-d) on bromination followed by dehydrobromination gave 2-(3′-chromonyl)-3-nitrochromones (Va-d). Their structures were supported by their elemental analyses and spectral data (Table 1).

The chromanone derivatives III and IV in their IR spectra showed $\nu_{C=O}$ around 1700 and 1640 cm^{-1} due to chromanone and chromone carbonyls respectively. However, chromone derivative exhibited $\nu_{C=O}$ around 1650 and 1640 cm^{-1}.

Antimicrobial activity

Of the above compounds tested, IVa (R^1 = 6-Cl, R^2 = 6-Cl) inhibited the growth of *A. niger* at 50 ppm and that of *E. coli* and *S. aureus* at 100 ppm concentration.

Melting points were taken in open capillaries in a sulphuric acid-bath and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer infrared 337 spectrophotometer (ν_{max} in cm^{-1}), UV spectra on a Beckmann D B spectrophotometer and mass spectra on a Hitachi RMU 6 L instrument.



†For Part I of the series, see ref. 1.

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Table 1—Characterization Data of Compounds III-V*

Compd	R^1	R^2	m.p. °C	Yield (%)	Mol. formula	Found (%) (Calc.) C	H	N	UV, nm (log ε)	MS: (*m/z*) relative intensity (%)
IIIa	6-Me	6-Cl	242	80	$C_{19}H_{12}O_6NCl$	59.3 (59.1	3.2 3.1	3.7 3.6)	314 (4.13)	383 (7, M^+), 353 (12), 339 (100), 338 (56), 310 (61), 205 (77), 155 (30), 135 (53), 134 (68)
IIIb	6-Me	6-Me	224	75	$C_{20}H_{15}O_6N$	65.9 (65.8	4.2 4.1	3.8 3.8)	314 (4.08)	—
IIIc	6-Cl	6-Cl	221	78	$C_{18}H_9O_6NCl_2$	53.4 (53.2	2.3 2.2	3.5 3.4)	316 (4.16)	—
IIId	7-MeO	6-Cl	212	75	$C_{19}H_{12}O_7NCl$	56.8 (56.8	3.0 3.0	3.5 3.5)	305 (4.14)	—
IVa	6-Me	6-Cl	214	55	$C_{19}H_{14}O_6NBrCl$	49.2 (49.1	2.5 2.4	3.1 3.0)	340 (3.83)	463 (2, M^+), 417 (36), 384 (22), 351 (36), 337 (44), 219 (40), 155 (29), 154 (37), 135 (33), 134 (46)
IVb	6-Me	6-Me	205	43	$C_{20}H_{14}O_6NBr$	54.2 (54.1	3.2 3.2	3.3 3.2)	338 (3.84)	—
IVc	6-Cl	6-Cl	242	52	$C_{18}H_8O_6NCl_2Br$	44.7 (44.5	1.7 1.7	2.8 2.9)	342 (3.82)	—
IVd	7-MeO	6-Cl	181	45	$C_{19}H_{11}O_7NClBr$	47.5 (47.5	2.3 2.3	2.9 2.9)	344 (3.08)	—
Va	6-Me	6-Cl	288	55	$C_{19}H_{12}O_6NCl$	59.2 (59.5	2.7 2.6	3.7 3.7)	301 (4.51)	383 (4, M^+), 351 (9), 337 (100), 281 (11), 155 (34), 154 (23), 135 (19), 134 (32)
Vb	6-Me	6-Me	262	45	$C_{20}H_{13}O_6N$	66.2 (66.1	3.5 2.6	4.0 3.9)	300 (4.42)	—
Vc	6-Cl	6-Cl	294	50	$C_{18}H_7O_6NCl$	53.5 (53.5	1.7 1.7	3.5 3.5)	303 (4.42)	—
Vd	7-MeO	6-Cl	275	47	$C_{19}H_{10}O_7NCl$	57.1 (57.1	2.6 2.5	3.6 3.5)	301 (4.52)	—

*PMR spectra of the compounds could not be recorded as they were very poorly soluble in nmr solvents.

2-(3'-Chromonyl)-3-nitrochromanones (IIIa-d): General procedure

To a solution of I (0.005 mol) in gl. acetic acid (10 ml) was added appropriate chromone-3-carboxaldehyde (II; 0.005 mol), the mixture warmed on a water-bath to get a clear solution and ammonium acetate (0.5 g) added to it. The reaction mixture was heated under reflux for 4 min over a low flame. A pale yellow crystalline solid started separating and the reaction was completed in an another min. The precipitate was filtered hot, washed with gl. acetic acid and recrystallised from a large excess of gl. acetic acid as shining colourless fibres (Table 1).

3-Bromo-2-(3'-chromonyl)-3-nitrochromanones (IVa-d): General procedure

To a solution of III (0.005 mol) in excess of gl. acetic acid was added a solution of bromine (0.005 mol.) in gl. acetic acid (5 ml) and the reaction mixture refluxed for 2 hr, cooled to room temperature and excess of acetic acid removed under suction. The colourless needles separated were filtered and recrystallised from chloroform as colourless glistening plates (Table 1).

1-(3'-Chromonyl)-3-nitrochromones (Va-d): General procedure

A suspension of IV in dry pyridine (10 ml) was heated under reflux for 40 min and cooled to room temperature. The compound that separated was filtered and recrystallised from acetone (Table 1).

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Bromination, Hydrolysis & Oxidation of 1-Phenyl-1*H*-pyrazolo[3,4-*b*]quinoxaline (1-Phenylflavazole)

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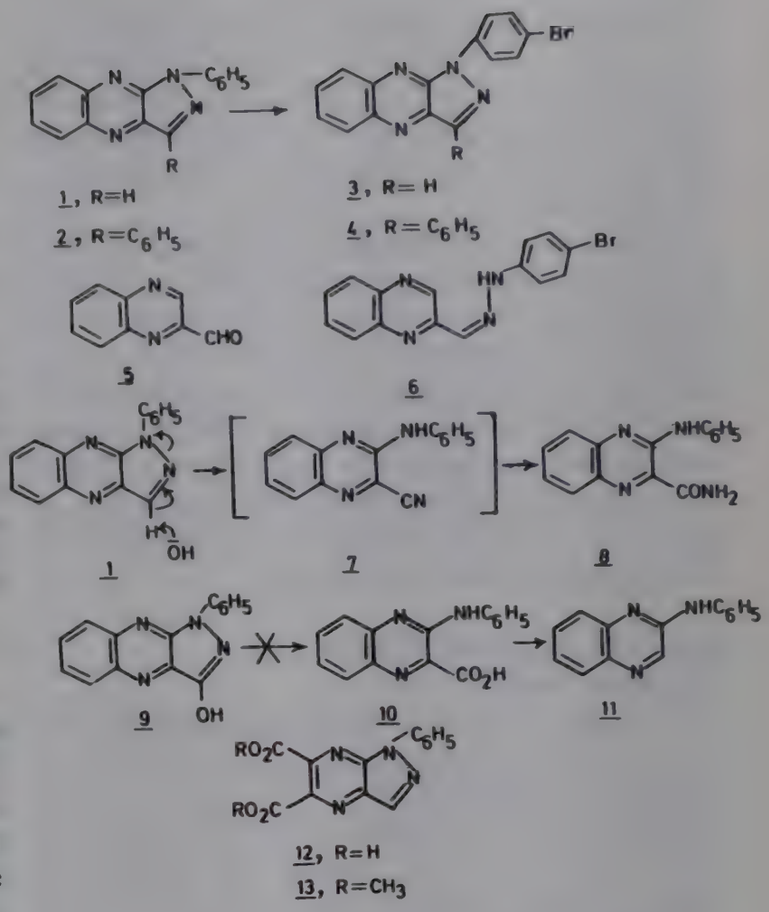
Bromination of 1-phenylflavazole (1-phenyl-1*H*-pyrazolo-[3,4-*b*]quinoxaline) (**1**) and 1,3-diphenylflavazole (**2**) gives a single product in each case, the bromination taking place at *para*-position of the 1-phenyl group. Hydrolysis of **1** with NaOH or $NaBH_4$ in boiling isopropanol ruptures the heterocyclic ring producing 2-anilinoquinoxaline-3-carboxylic acid (**10**) or its amide (**9**). Oxidation of **1** with $KMnO_4$ produces 1-phenylpyrazolo[3,4-*b*]pyrazine-5,6-dicarboxylic acid (**12**) which is characterised as its dimethyl ester (**13**).

The flavazole (1*H*-pyrazolo[3,4-*b*]quinoxaline) derivatives[1-3] have gained importance recently because of their potential biological activities[4,5]. Although a number of reactions of flavazoles have been studied, most of them pertain to the carbohydrate side chain attached to the 3-position[1,2]. We now report the bromination of 1-phenyl- and 1,3-diphenyl-flavazoles, and the oxidation reaction of 1-phenylflavazole. In addition, the flavazole has been shown to undergo hydrolysis with ring cleavage under alkaline conditions.

Treatment of 1-phenylflavazole (**1**)[6] using bromine in gl. AcOH gave 1-(*p*-bromophenyl)flavazole (**3**) in 92% yield. The structure of **3** was established by its unambiguous synthesis involving cyclisation of quinoxaline-2-carboxaldehyde *p*-bromophenyl-hydrazone (**6**) in the presence of azobenzene. Compound **6** was prepared from quinoxaline-2-carboxaldehyde (**5**)[7] and *p*-bromophenylhydrazine[8]. Treatment of 1,3-diphenylflavazole (**2**)[9] with bromine in AcOH also provided a single product (**4**) in 94% yield, the bromination taking place at *para*-position of the 1-phenyl group.

1-Phenylflavazole (**1**) being a stable aromatic system is not easily reduced. Thus, attempts to reduce **1** with $NaBH_4$ in methanol and $LiAlH_4$ in ether at room temperature were not successful. However, treatment of **1** wih$NaBH_4$ in boiling isopropanol for a long time produced a new compound in 58% yield, which was subsequently shown to be 2-anilinoquinoxaline-3-carboxamide (**9**) on the basis of its spectral data, elemental analysis and chemical reactions. Alkaline hydrolysis of **9** followed by acidification with HCl



provided the corresponding carboxylic acid (**10**)[10] which underwemt decarboxylation on heating to give 2-anilinoquinoxaline (**11**)[11]. Acid hydrolysis of **9** using conc. HCl also provided **11** in one step involving both hydrolysis and decarboxylation.

The formation of **8** from **1** by reaction with sodium borohydride may be explained as follows: As the system is not easily reduced, traces of OH^- ions present in solution abstract proton from the 3-position of **1** resulting in the formation of the nitrile **7** by a concerted reaction. The cyanide group in **7** undergoes partial hydrolysis to give the carboxamide **9** by the small amount of water present in isopropanol. Although there is no direct evidence for the formation of **7**, the following points may be cited in support of this mechanism. First, a small amount of the carboxylic acid **10** was also formed in this reaction, which was precipitated on acidification of the mother liquor obtained after separation of **8**. Secondly, treatment of **1** itself with boiling 10% aq. NaOH resulted in the hydrolysis of **1** producing the carboxylic acid **10** in 83% yield. Finally, 1-phenyl-3-hydroxy-flavazole (**9**)[12], another possible intermediate in this reaction, was not converted into the amide **8** when treated with $NaBH_4$ in boiling isopropanol.

Although the oxidation of unsubstituted flavazole to pyrazolo[3,4-*b*]pyrazine-5,6-dicarboxylic acid has been carried out[13], the oxidation of 1-phenylflavazole **1** has not been reported. We, therefore, carried out the oxidation of **1** with a neutral solution of $KMnO_4$ at 120° to give 1-phenylpyrazolo[3,4-*b*]pyrazine-5,6-dicarboxylic acid (**12**) in 62% yield. This acid was also characterised as its dimethyl ester (**13**), prepared by the treatment of **12** with diazomethane in methanol at a low temperature.

Melting points are uncorrected. TLC was performed on 5 × 20 cm glass plates coated with silica gel G using chloroform as irrigant unless otherwise stated. Mass spectra were recorded on a Varian MAT CH 7 mass spectrometer, PMR spectra in $CDCl_3$ on a Hitachi R-600 FT NMR spectrometer using TMS as internal standard (chemical shifts in δ, ppm), IR on a Perkin-Elmer model 682 grating spectrophotometer (ν_{max} in cm^{-1}) and UV spectra in methanol on a Hitachi model 200 spectrophotometer (λ_{max} in nm).

Quinoxaline-2-carboxaldehyde p-bromophenylhydrazone (**6**)

A solution of quinoxaline-2-carboxaldehyde (**5**)[7] (3.9 g, 0.025 mol) and *p*-bromophenylhydrazine[8] (4.7 g, 0.025 mol) in methanol (50 ml) was stirred at room temperature for 1 hr, diluted to 250 ml with water, stirred further for 2 hr, cooled and precipitated product filtered, washed with water, dried and recrystallised from methanol to give **6** (6.0 g, 73%), m.p. 225° (d) (Found: C, 55.3; H, 3.7; N, 17.4. $C_{15}H_{11}BrN_4$ requires C, 55.1; H, 3.4; N, 17.1%).

1-(*p-Bromophenyl*)*flavazole* {1-(*p-Bromophenyl*)-1*H-pyrazolo*[3,4-*b*]*quinoxaline*} (**3**)

(*a*) *By bromination of* **1**

A solution of **1** (0.5 g, 0.002 mol) in gl. AcOH (100 ml) was mixed with 3 ml of a 20% (v/v) bromine in AcOH and the mixture stirred for 48 hr at room temperature. Completion of the reaction was checked by TLC. Thereafter, it was diluted to 250 ml with water, the precipitate filtered, dried and recrystallised from 75% AcOH to give **3** (600 mg, 92%) m.p. 212°; UV: 271 ($\varepsilon 1.07 \times 10^5$), 333 ($\varepsilon 2.26 \times 10^4$) (Found: C, 55.2; H, 3.0; N, 17.2. $C_{15}H_9BrN_4$ requires C, 55.4; H, 2.8; N, 17.2%).

(*b*) *From quinoxaline-2-carboxaldehyde p-bromophenylhydrazone* (**6**)

A mixture of **5** (650 mg, 0.002 mol), azobenzene (370 mg, 0.002 mol), 60% aq. 1-propanol (50 ml), gl. AcOH (0.5 ml) and 1 *N* HCl (5 ml) was heated under reflux for 10 hr on a boiling water-bath, cooled, the solid filtered, washed with water followed by cold 50% aq. 1-propanol, dried and recrystallised from 70% AcOH to give **3** (510 mg, 78%), m.p. 212°, identical (m.m.p.) with that obtained above.

1-(*p-Bromophenyl*)-3-*phenylflavazole* {1-(*p-Bromophenyl*)-3-*phenyl*-1*H-pyrazolo*-[3,4-*b*]*quinoxaline*} (**4**)

To a solution of 1,3-diphenylflavazole (**2**)[9] (320 mg, 0.001 mol) in gl. AcOH (100 ml) was added 2.0 ml of a 20% (v/v) bromine solution in AcOH and the mixture stirred at room temperature for 24 hr. After the reaction was found to be complete by TLC using hexane-benzene (3:2) as irrigant, the reaction mixture was diluted to 250 ml with water, cooled, and the precipitate filtered, washed with water, dried and recrystallised from 90% AcOH to give **4** (380 mg, 94%), m.p. 246°, MS: *m/z* 400 and 402 (M^+); UV: 261.2 ($\varepsilon 3.4 \times 10^5$), 289.4 ($\varepsilon 3.06 \times 10^5$), 336.6 ($\varepsilon 7.38 \times 10^4$) (Found: C, 63.2; H, 3.3; N, 14.0. $C_{21}H_{13}BrN_4$ requires C, 62.9; H, 3.3; N, 14.0%).

2-*Anilinoquinoxaline-3-carboxamide* (**8**)

A solution of **1** (370 mg, 0.0015 mol) in isopropanol (200 ml) was mixed with powdered $NaBH_4$ (1 g, in 200 mg portions), and the mixture heated under reflux for 80 hr on a boiling water-bath. The unreacted $NaBH_4$ was decomposed by the addition of a few ml of water. The isopropanol was removed under reduced pressure and 50 ml of water added to the residue. The precipitate was filtered, washed with water, dried, and found by TLC to contain two compounds which were separated by column chromatography over silica gel using benzene as eluent to the starting material **1** (50 mg, 13.5%) m.p. and m.m.p. 152°, and **8** (230 mg, 58%), m.p. 220° (from $CHCl_3$-hexane); MS: *m/z* 264 (M^+), 220 ($M^+ - CONH_2$), 91 ($C_6H_5N^+$), 77 ($C_6H_5^+$); IR (KBr): 3410 and 3320 (NH_2), 1680 (C=O); UV: 220.4 ($\varepsilon 1.01 \times 10^5$), 288.2 ($\varepsilon 1.2 \times 10^5$) (Found: C, 68.4; H, 4.8; N, 21.4. $C_{15}H_{12}N_4O$ requires C, 68.6; H, 4.6; N, 21.2).

2-*Anilinoquinoxaline-3-carboxylic acid* (**10**)

(*a*) *From the mother liquor of* **8**

The mother liquor after separating **8** was cooled, acidified with HCl and extracted with $CHCl_3$. The extract was dried (Na_2SO_4) and evaporated to dryness under reduced pressure. The yellow residue was recrystallised from chloroform-pentane to give **10** (40 mg, 10%), m.p. 165° (d), IR (CCl_4): 3300-2800 (broad) and 1730; UV of sodium salt: 283.6 ($\varepsilon 9.7 \times 10^4$) and 398 ($\varepsilon 1.8 \times 10^4$) [lit.[10] 285 ($\varepsilon 2.9 \times 10^4$) and 395 ($\varepsilon 6250$)].

(*b*) *By alkaline hydrolysis of* **8**

A mixture of **8** (100 mg, 0.0004 mol), 25 ml of 10% NaOH solution (25 ml) and 1-propanol (20 ml) was heated under reflux for 4 hr, concentrated to 25 ml,

cooled in ice, acidified with HCl and extracted with $CHCl_3$. The extract was dried (Na_2SO_4), evaporated to dryness *in vacuo* and the residue recrystallised from $CHCl_3$-pentane to give **10** (85 mg, 85%), identical (m.m.p., UV) with that obtained above.

(*c*) *By hydrolysis of* **1**

A mixture of **1** (200 mg, 0.0008 mol), 10% NaOH solution (25 ml) and 1-propanol (20 ml) was heated under reflux for 25 hr, and workedup as in (b) to give **10** which recrystallised from $CHCl_3$-hexane, identical (m.m.p., UV) with that obtained by the above two methods.

2-*Anilinoquinoxaline* (**11**)

(*a*) *By decarboxylation of* **10**

The acid **10** (100 mg, 0.0004 mol) was heated in a test tube at 200° for 30 mins in an oil-bath. The mixture was purified by column chromaography over silica gel using $CHCl_3$ as eluent to give **11** which recrystallised from $CHCl_3$-hexane, yield 60 mg (72%) m.p. 137° (lit.[11], m.p. 137°).

(*b*) *By acid hydrolysis of* **8**

A mixture of **8** (100 mg, 0.0004 mol) and conc. HCl (15 ml) was heated under reflux for 4 hr, concentrated to 5 ml under reduced pressure, cooled in ice, neutralised with 10% NaOH solution and kept in a refrigerator overnight. The precipitate was filtered, washed with cold water, dried and recrystallised from $CHCl_3$-hexane to give **11** (70 mg, 84%), identical (m.p. and m.m.p. 137°) with that obtained above.

1-*Phenylpyrazolo*[3,4-*b*]*pyrazine*-5,6-*dicarboxylic acid* (**12**)

A suspension of finely powdered **1** (550 mg, 0.0002 mol) in a 4% aq. solution of $KMnO_4$ was boiled under reflux for 5 hr with vigorous stirring, and the excess permanganate destroyed by adding a few drops of CH_3OH. The mixture was filtered while hot through a sintered glass funnel and washed with 25 ml of water. The filtrate and washings were combined and concentrated to 50 ml under reduced pressure, cooled in ice and acidified with HCl. The solution was refrigerated overnight, filtered, washed with a little ice-cold water and recrystallised from hot water to give **12** (35 mg, 62%), m.p. 236° (d); MS: *m/z* 266 ($M^+ - H_2O$), 240 ($M^+ - CO_2$), 222 ($M^+ - H_2O - CO_2$), 194 ($M^+ - H_2O - CO - CO_2$), 77 ($C_6H_5^+$) (Found: C, 55.3; H, 3.0; N, 20.0. $C_{13}H_8N_4O_4$ requires C, 54.9; H, 2.8; N, 19.7%).

Dimethyl 1-*phenylpyrazolo*[3,4-*b*]*pyrazine*-5,6-*dicarboxylate* (**13**)

A mixture of 18 ml of 50% aq. KOH solution (10 ml) and ether (60 ml) was cooled to 5° and nitrosomethylurea (6.2 g) added to it with stirring. The ether layer containing diazomethane was immediately separated and added to a cold solution of **12** (280 mg, 0.001 mol) in CH_3OH (150 ml) and the mixture stirred for 1 hr. The solvent was removed under reduced pressure and the residue stirred with saturated $NaHCO_3$ solution, and extracted with ether. The etherial layer was dried (Na_2SO_4), evaporated to dryness and the residue recrystallised from CH_3OH to give **13** (270 mg, 87%) m.p. 140°; MS: *m/z* 312 (M^+), 281 ($M^+ - OCH_3$), 253 ($M^+ - COOCH_3$), 222 ($M^+ - OCH_3 - COOCH_3$), 194 ($M^+ - 2\ COOCH_3$), 77 ($C_6H_5^+$); NMR: 4.1 (6H, *s*, $2 \times OCH_3$), 7.6-8.3 (5H, *m*, C_6H_5), 8.65 (1H, *s*, H-3); UV: 268.6 ($\varepsilon\ 5.3 \times 10^5$) (Found: C, 57.6; H, 4.2; N, 17.8. $C_{15}H_{12}N_4O_4$ requires C, 57.7; H, 3.9; N, 18.0%).

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Synthesis & Hypolipidaemic Activity of Ethyl α-Methyl-α-[*p*-(benzosuber-1-yl/benzosuber-1-enyl)phenoxy]propionates & Their Derivatives‡

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Ethyl α-methyl-α-[*p*-(benzosuber-1-yl/benzosuber-1-enyl)-phenoxy]propionates (**7**, **13**) and their acids (**8**, **14**) have been prepared by treating 1-(*p*-hydroxyphenyl)benzosuberan/suberene (**4**, **11**) with ethyl α-bromoisobutyrate followed by hydrolysis. Compounds **7**, **8**, **13** and **14** reduce the level of serum cholesterol by 30, 26, 35 and 42% respectively.

Dihydro- and tetrahydro-naphthalene derivatives[1-3] form a class of hypolipidaemic agents of which nafenopin[4], α-methyl-α-[*p*-(1,2,3,4-tetrahydro-1-naphthyl)phenoxy]propionic acid (I) is a valuable drug for all types of hyperlipoproteinaemia. Recently, ethyl α-methyl-α-[*p*-(1-indanyl)-phenoxy]propionate (II) and its acid have also been reported to possess cholesterol and triglyceride lowering activity. To improve upon the activity of I and II, the related homologous benzosuberan derivatives (III) appeared attractive candidates as in their dreiding models, one of the spatial arrangements of III is superimposable to I (Fig. 1). In view of this, we report herein the synthesis and hypolipidaemic activity of ethyl α-methyl-α-[*p*-(benzosuber-1-yl/benzosuber-1-enyl)phenoxy]propionates and their derivatives.

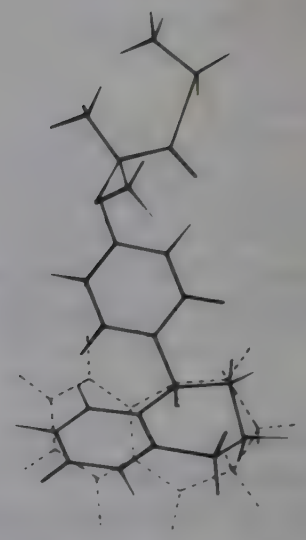
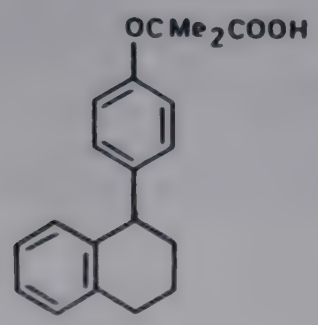


Fig. 1—Superimposition of nafenopin (I) over III (—, nafenopin; ---- benzosuberan)

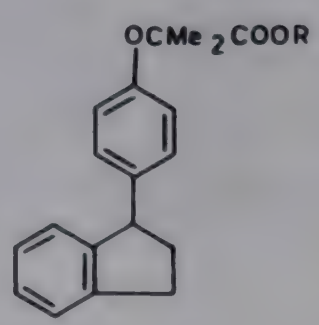
The reaction of benzosuber-1-ol (**2**)[6] with PhOH—HCl afforded, in analogy to earlier work[7], a mixture of 1-(*o*-hydroxyphenyl)(**3**) and 1-(*p*-hydroxyphenyl)(**4**)-benzosuberans (Scheme 1) which were separated on silica gel column.

The reported Grignard addition of PhMgBr and *p*-MeO—C_6H_4MgBr onto 1-benzosuberone (**1**) followed by treatment gave with *p*-TsOH 1-(phenyl/*p*-methoxyphenyl)benzosuber-1-enes (**9**, **10**)[8]. Demethylation of **10** with pyridine hydrochloride yielded 1-(*p*-hydroxyphenyl) derivative (**11**) Ac_2O-pyridine treatment of **3**, **4** and **11** yielded the corresponding acetates **5**, **6** and **12**. Alkylation of **4** and **11** with ethyl α-bromoinsobutyrate[9] in the presence of NaH in dry DMF furnished the title compounds, α, α-disubstituted propionates **7** and **13** respectively which on alkaline hydrolysis gave the acids **8** and **14**. Similarly, **11** with ethyl bromoacetate in the presence of K_2CO_3—Me_2CO yielded the ethyl acetate derivative **15** which on hydrolysis gave the corresponding (**16**).

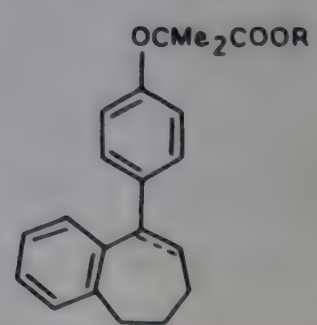


I.

(Nafenopin)

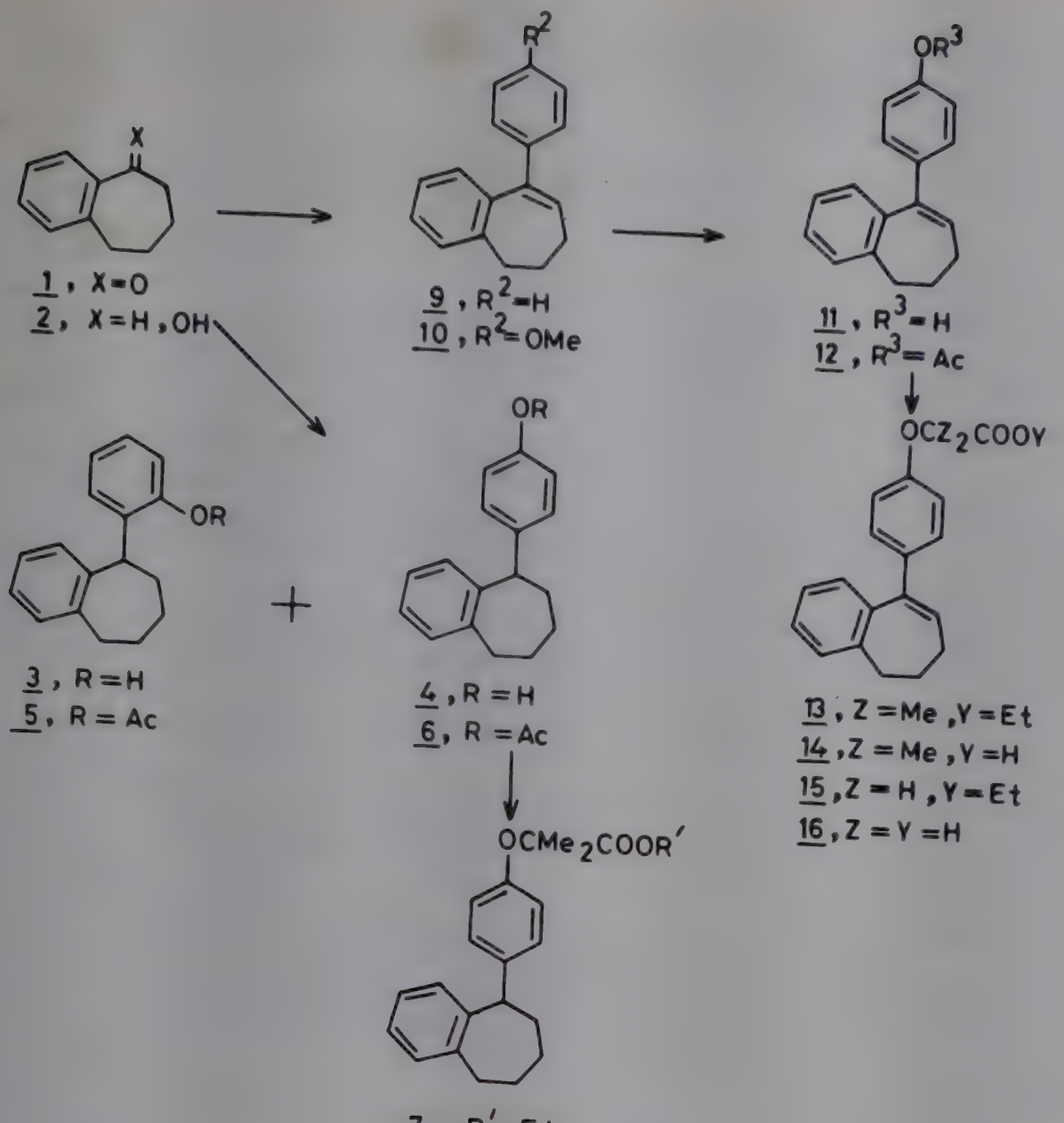


II.



III.

‡CDRI Communication No. 3597



SCHEME 1

Biological activity

The hypolipidaemic activity of the compounds was evaluated in Triton-treated rats by the described procedure[10]. Adult charles foster strain rats (approximately weighing 200-250 g each) were housed under standard laboratory conditions and kept on fast but given water *ad libitum* on the day of treatment. In the evening at 4 p.m. all the animals under test received Triton WR-1339, 400 mg/kg bW intraperitoneally, and after 15 min the test compound (50 mg/kg bW) and the standard drug nicotinic acid (500 mg/kg bW) were given intraperitoneally to two separate groups (keeping six animals in each group). A group of six animals treated with Triton but given no test compound served as the control group. Eighteen hours after the treatment, blood samples were taken from the tail for the estimation of serum cholesterol.

In the above test compounds **7**, **8**, **13** and **14** at 50 mg/kg i.p. dose produced the lowering in serum cholesterol by 30%, 26%, 35% and 42% respectively whereas nicotinic acid, a reference drug, at 500 mg/kg dose caused a lowering in serum cholesterol by 46%. Clofibrate even at 200 mg/kg dose produced only 14.6% lowering in serum cholesterol. A dosewise comparison with the reference drug shows that the compounds tested are significantly active. Regarding structure activity relationships, the benzosuberene derivatives are more active than the benzosuberans and amongst benzosuberenes, acid **14** is more potent than its ester (**13**).

Melting points were taken in a Toshniwal melting point apparatus and are uncorrected. Purity of the compounds was checked on silica gel TLC plates. IR spectra were recorded on a Perkin-Elmer 157 spectrophotometer (ν_{max} in cm^{-1}) and PMR and Mass spectra were recorded as referred in Table 1.

1-(*o-/p-Hydroxyphenyl*)*benzosuberans* (**3**, **4**)

Dry HCl gas was passed into a cold solution of 1-benzosuberol (**2**)[6] (4.0 g, 24 mmol) and PhOH (6.76 g,

Table 1—Characterization Data of 1-Substituted-phenyl-benzosuber-1-enes/suberans

Compd[a]	Yield (%)	m.p.[b] °C	Mol. formula (Mol wt)[c]	PMR($CDCl_3$)[d] δ, ppm	M^+, m/z (rel. intensity, %)[e]
3	20	82-83	$C_{17}H_{18}O$ (238)	1.90 (*m*, 6H, 2-CH_2, 3-CH_2 and 4-CH_2), 2.80 (*t*, 2H, 5-CH_2, J=6 Hz), 4.44 (*t*, 1H, C_1-H, J=6 Hz), 6.60-7.0 (*m*, 8H, Ar−*H*)	238 (100), 239 (18.9), 237 (14.5), 209 (21.3), 144 (95.9), 131 (49.5), 115 (20.0), 107 (27.5)
4	42	89-90	$C_{17}H_{18}O$ (238)	2.72 (*t*, 2H, 5-CH_2, J=6 Hz), 4.05 (*t*, 1H, C_1-H, J=6 Hz), 6.55 (*dd*, 2H, Ar−*H*, *o*- to OH, J=9 & 3 Hz), 6.70-6.90 (*m*, 6H, Ar−*H*)	238 (40.8), 239 (6.8), 144 (42.8), 131 (53.6), 31 (27.9), 28 (100)
5	85	77-78	$C_{19}H_{20}O_2$ (280)	1.92 (*s*, 3H, $COCH_3$), 2.0 (*m*, 6H, 2-CH_2, 3-CH_2 and 4-CH_2), 2.78 (*m*, 2H, 5-CH_2), 4.30 (*m*, 1H, C_1-H), 6.80-7.25 (*m*, 8H, Ar−*H*)	280 (26.2), 238 (100), 144 (72.3)
6	80	95	$C_{19}H_{20}O_2$ (280)	2.16 (*s*, 3H, $COCH_3$), 2.72 (*t*, 2H, 5-CH_2, J=6 Hz), 4.15 (*t*, 1H, C_1-H, J=5 Hz)	280 (24.1), 281 (5.2), 238 (100), 144 (68.2)
7	53	Oil	$C_{23}H_{28}O_3$ (352)	1.20 (*t*, 3H, CH_2-CH_3, J=7 Hz), 1.55 (*s*, 6H, 2×CH_3), 4.12 (*q*, 2H, CH_2-CH_3, enveloping C_1-H proton J=7 Hz)	352 (34.3), 353 (8.9), 279 (20.5), 238 (60.3), 144 (100)
8	80	Oil	$C_{21}H_{24}O_3$ (324)	1.56 (*s*, 6H, 2×CH_3), 4.12 (*t*, 1H, C_1-H, J=5 Hz), 6.65-7.20 (*m*, 8H, Ar−*H*)	324 (29.2), 325 (7.2), 238 (59.5), 144 (100)
11	86	Oil	$C_{17}H_{16}O$ (236)	2.57 (*t*, 2H, 5-CH_2, J=6 Hz), 6.23 (*t*, 1H, C_2-H, J=7 Hz), 6.64 (*d*, 2H, Ar−*H*, *o*- to OH, J=9 Hz), 7.25 (*m*, 6H, Ar−*H*)	236 (100), 237 (18.9), 235 (23.8), 208 (59.6), 170 (45.6), 144 (30.8), 129 (45.2)
12	82	80-81	$C_{19}H_{18}O_2$ (278)	2.18 (*s*, 3H, $COCH_3$), 2.55 (*t*, 2H, 5-CH_2, J=6 Hz), 6.28 (*t*, 1H, C_2-H, J=7 Hz), 7.0 (*m*, 8H, Ar−*H*)	278 (26.2), 236 (100)
13	40	Oil	$C_{23}H_{26}O_3$ (350)	1.12 (*t*, 3H, CH_2-CH_3, J=7 Hz), 1.49 (*s*, 6H, 2×CH_3), 4.10 (*q*, 2H, CH_2-CH_3, J=7 Hz), 6.22 (*t*, 1H, C_2-H, J=7 Hz), 6.60-7.10 (*m*, 8H, Ar−*H*)	350 (19.1), 351 (4.9), 236 (78.2), 208 (99), 170 (95.1), 28 (100)
14	80	Oil	$C_{21}H_{22}O_3$ (322)	1.48 (*s*, 6H, 2×CH_3), 6.72-7.20 (*m*, 8H, Ar−*H*), 7.50-7.80 (*bh*, 1H, CO_2H)	322 (1.6), 236 (4.5), 208 (3.7), 94 (100), 84 (82.1)
15	62	Oil	$C_{21}H_{22}O_3$ (322)	1.18 (*t*, 3H, CH_2-CH_3, J=7 Hz), 4.12 (*q*, 2H, CH_2-CH_3, J=7 Hz), 4.50 (*s*, 2H, OCH_2), 6.24 (*t*, 1H, C_2-H, J=7 Hz), 6.90 (*m*, 8H, Ar−*H*)	322 (26.9), 323 (6.2), 260 (59.5), 258 (60.2), 107 (100), 77 (100)
16	66	Oil	$C_{19}H_{18}O_3$ (294)	2.48 (*t*, 2H, 5-CH_2, J=6 Hz), 4.20 (*s*, 2H, OCH_2), 6.22 (*t*, 1H, C_2-H), J=6 Hz), 6.92 (*m*, 8H, Ar−*H*)	294 (52.7), 232 (61.1), 260 (63.4), 107 (95), 77 (100)

[a]Numbers refer to the compounds described in Scheme 1.
[b]Compounds **3-6** and **12** were crystallized from MeOH and oily compounds **7**, **8**, **11**, **13-16** were purified by column chromatography over silica gel G using C_6H_6 as eluant.
[c]Carbon and hydrogen analyses of the compounds **3-16** were found within ±0.4% of the theoretical values.
[d]PMR spectra were recorded on Perkin-Elmer R-32 and Varian EM-360L instruments using TMS as internal reference (chemical shift in δ, ppm).
[e]Mass spectra were run on a Jeol D-300 instrument fitted with a direct inlet system.

72 mmol) in abs. MeOH (40 ml) for 30 min and the mixture kept at room temperature for 160 hr. MeOH was removed by distillation and the residue extracted with ether. The extract was washed with water, satd CH_3COONa solution, dried (Na_2SO_4) and concentrated to dryness. The residue, thus obtained, was treated with hot 10% NaOH solution and the sodium salt filtered and washed with ether. Acidification with 2*N* HCl gave free phenols as a mixture of 1-(*o*- and *p*-hydroxyphenyl) isomers (**3** and **4**). The mixture was purified by column chromatography over silica gel using C_6H_6-hexane as eluant to get **3** [yield 1.2 g (20%), m.p. 82°, IR(KBr): 3250 (OH)] and **4** [yield 2.8 g (42%), m.p. 89-90°. IR(KBr): 3220 (OH)].

1-(*o-Acetoxyphenyl*)*benzosuberan* (**5**)

To a stirred solution of **3** (0.24 g, 1 mmol) in pyridine (5 ml) was added Ac_2O (0.10 g, 1 mmol) and the mixture stirred overnight at room temperature. The

reaction mixture on usual work-up gave **5** which crystallised from MeOH, yield 0.25 g (85%), m.p. 77°, IR(KBr): 1760 ($COCH_3$).

Similarly, 1-(*p*-acetoxyphenyl)benzo-suberan and suber-1-ene (**6** and **12**) were prepared from **4** and **11** respectively.

Ethyl *α-methyl-α-[p-(1-benzosuberyl)-phenoxy]propionate* (**7**)

A suspension of **4** (1.1 g, 5 mmol), $BrCMe_2CO_2Et$ (0.42 g, 5 mmol) and NaH (0.25 g, 10 mmol, 50% dispersion) in dry DMF (15 ml) was heated under stirring at 120° for 24 hr. It was filtered, the filtrate concentrated under reduced pressure and the residue taken up in ether. The extract was washed with water, dried (Na_2SO_4) and concentrated. The crude oil (0.9 g) was purified by column chromatography over silica gel using C_6H_6-hexane (1:1) as eluant to get **7** as an oil, yield 0.4 g (53%), IR(neat): 1730 (CO_2Et).

Similarly, ethyl α-methyl-α-[*p*-(benzosuber-1-enyl)phenoxy]propionate (**13**) was prepared from **11**.

α-Methyl-α-[p-(1-benzosuberyl)phenoxy]propionic acid (**8**)

A suspension of **7** (0.35 g, 1 mmol) in 4% methanolic KOH (5 ml) was stirred at room temperature for 2 hr and then concentrated. The residue was taken-up in water and aq. phase washed with ether. The acid was liberated with dil. HCl, extracted with ether, dried (Na_2SO_4) and concentrated to get **8** as an oil, yield 0.25 g (80%), IR(neat): 1700 (CO_2H).

Similarly, α-methyl-α-[*p*-(benzosuber-1-enyl)phenoxy]propionic acid (**14**) and [*p*-benzosuber-1-enyl)phenoxy]acetic acid (**16**) were prepared from **13** and **15**, respectively.

1-*(p-Hydroxyphenyl)benzosuber*-1-*ene* (**11**)

A mixture of **10** (0.25 g, 1 mmol) and py. HCl (6 g) was heated at 220° for 30 min. The reaction mixture on usual work-up gave an oil which was purified by column chromatography over silica gel using C_6H_6 as eluant to afford **11**, yield 0.20 g (88%) IR(neat): 3400 (OH).

Ethyl α-[p-(benzosuber-1-enyl)phenoxy]acetate (**15**)

A suspension of **11** (0.7 g, 3 mmol), K_2CO_3 (0.41 g, 3 mmol) and $BrCH_2CO_2Et$ (0.5 g, 3 mmol) in dry Me_2CO (15 ml) was refluxed under stirring for 15 hr. The reaction mixture on work-up gave an oil which was purified by silica column using C_6H_6 as eluant to give **15** as an oil, yield 0.61 g (62%), IR(neat): 1765 (CO_2Et).

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Studies on Potential Antibacterial & Chelating Agents: Part I—Synthesis, Physicochemical Properties & Antibacterial Screening of Some Benzimidazoles

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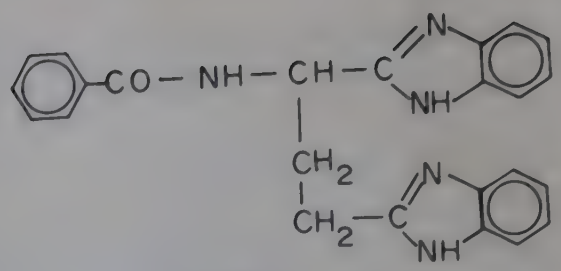
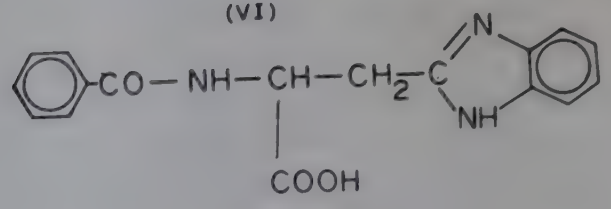
Six properly substituted benzimidazoles (I-VI) suitable for chelation have been synthesised from benzoylamino acids by condensation with *o*-phenylenediamine following Phillips and fusion methods. Dissociation constants of the benzoyl derivatives of glycine, (*dl*)-α-alanine, β-alanine, L-(−)-aspartic acid, L-(+)-glutamic acid and the six protonated benzamidobenzimidazoles (I-VI) in water-dioxane (1:1) at constant ionic strength ($\mu = 0.5$) at 20° ±0.1° have been determined by potentiometric titration. Structures of I-VI have been established on the basis of their elemental analysis, synthetic route, IR and PMR spectra and *pk** values. Some of the compounds show significant antibacterial activity against gram +ve organisms only whereas corresponding sulphonamidobenzimidazoles are active against the gram −ve organism *E. coli*.

Some biologically important benzimidazole derivatives of N-benzenesulphonylamino acids have been synthesised and found to be active against gram −ve bacteria[1]. They are so designed as to act as ligand and their complexation characteristics[2] have been studied. The biological activities[3-6] and complexation characteristics[7-9] of benzoylamino acids have been taken up very recently by different workers. In order to make a comprehensive study between the sulphonamidobenzimidazoles and benzamidobenzimidazoles with special reference to their antibacterial activity, complexation characteristics and antibacterial activity of the metal complexes, synthesis of benzamidobenzimidazoles has now been undertaken. In this note we describe the synthesis and antibacterial activity of a number of benzimidazole derivatives of N-benzoylamino acids, viz. 2-benzamidomethylbenzimidazole(I), 2-(α-benzamido)ethylbenzimidazole(II), 2-(β-benzamido)ethylbenzimidazole (III), α-benzamido-β-(2-benzimidazolyl)-L-(−)-propionic acid (IV), 1-benzamido-1,2-bis(2′-benzimidazolyl)ethane (V), and 1-benzamido-1,3-bis(2′-benzimidazolyl)propane (VI) following Phillips[10] and fusion[11] methods.

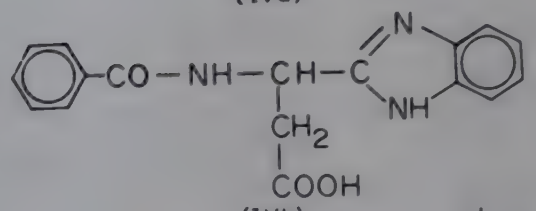
The benzimidazoles I-III were obtained in 45-70% yield but the yield of IV, V and VI was very poor. Higher temperature (fusion method) and longer reaction period (Phillips method) were necessary for synthesis of these compounds. However, under these conditions decomposition of the products took place resulting in lower yield of the benzimidazoles. While synthesising I, the unreacted compounds formed a salt if the reaction period was lowered.



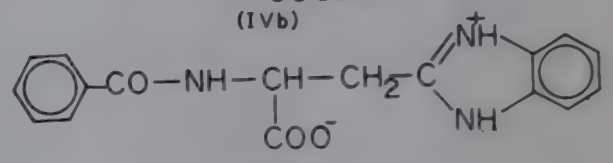
(VI)



(IVa)



(IVb)



(A)

The N-benzoyl derivatives of glycine ($R^b_mH_2$), (*dl*)-α-alanine ($R^b_{e\alpha}H_2$), β-alanine ($R^b_{e\beta}H_2$), L-(−)-aspartic acid ($R^b_AH_3$) and L-(+)-glutamic acid ($R^b_GH_3$) were prepared by reacting benzoyl chloride with the corresponding amino acids in the presence of alkali at ~60°. The reaction mixture was cooled and acidified with 9*N* H_2SO_4 to get the corresponding N-benzoyl derivative as a white compound which recrystallised from water. These benzamidobenzimidazoles were practically insoluble in water, and therefore, water-dioxane (1:1) was selected to determine their dissociation constants. The acidity of the monobasic acids was found to decrease in the order: $R^b_mH_2 > R^b_{e\alpha}H_2 > R^b_{e\beta}H_2$ and that of diabasic acids in the order: $R^b_AH_3 > R^b_GH_3$. This is due to interpolation of methylene group and the presence of $-CH_3$ group. This trend was also followed in the case of protonated benzimidazoles (Table 1).

Similar trend has been observed in the case of sulphonamide derivatives[15,16]. These values are useful in elucidating the structure of the monobenzimidazole derivative of $R^b_AH_3$ which may be represented by any one of the two alternative structures IVa and IVb. By comparing the pk^*_{COOH} values of IV with those of the starting materials $R^b_AH_3$, $R^b_mH_2$, $R^b_{e\alpha}H_2$ and $R^b_{e\beta}H_2$, and $pk^*_{\text{benzimidazolium ion}}$ of IVH^+ with those of IH^+,

Table 1—Analytical Data of the Various Compounds Prepared

Compound	Yield (%)	Eq wt Found (Calc.)	m.p. °C (lit.)	Found (%) (Calc.)			*pk** values of acids/ protonated species (±0.02)	
					H	N	*pk** 2	*pk** 1
$R^b_mH_2$	>80	178.9	186	—	—	—	—	4.68
		(179)	(187)	—	—	—	—	4.80
$R^b_{e\alpha}H_2$	>80	193.0	115					
		(193.0)						
$R^b_{e\beta}H_2$	>80	194.0	83	—	—	—	—	5.43
		(193.0)						
$R^b_AH_3$	>80	118.70	188	—	—	—	3.02	5.60
		(118.5)	(185)					
$R^b_GH_3$	>70	124.8	121	—	—	—	3.27	6.03
		(125.5)	(138)					
I 12.7*	55	288.0†	218	71.8	5.2	16.7	—	4.55
(12.4)		(287.5)		(71.7)	(5.2)	(16.7)		
II 11.4*	70	302.5†	245	72.6	5.8	15.8	—	4.76
(11.8)		(301.5)		(72.5)	(5.7)	(15.9)		
III 11.5*	41	303.0†	266(d)	72.0	5.6	15.7	—	5.35
(11.8)		(301.5)		(72.5)	(5.7)	(15.9)		
IV 10.4*	30	307.8	270(d)	65.8	4.8	13.6	3.70	6.18
(10.3)		(309.0)		(66.0)	(4.9)	(13.6)		
V 15.9*	25	228.4†	170(d)	72.1	5.0	18.1	2.76	4.84
(15.6)		(227.0)		(72.4)	(5.0)	(18.4)		
VI 15.3*	very	233.3†	135	72.7	5.1	17.5	—	—
(15.2)	low	(234.0)		(72.9)	(5.3)	(17.7)		

*Percentage of chlorine in hydrochloride; Calc. values in parentheses
†Eq wt of the hydrochloride

IIH^+ and $IIIH^+$ (Table 1), it becomes obvious that compound IV is actually IVa. Dibenzimidazole derivative(V) was ultimately formed under reflux for a longer period. The IR spectral data lent further support to the assigned structure IVa as it did in earlier cases[17–20]. A slight shift in $\nu C=N$ and heterocyclic breathing modes was associated with the protonation of one of the nitrogens of the imidazole ring. $R^b_AH_3$ showed a strong band at 1695 cm^{-1} due to COOH groups, which was absent in the IR spectrum of IV. In addition, COO^- asymmetrical and symmetrical stretching bands were observed at 1600 and 1390 cm^{-1} respectively, which indicated the zwitterion structure (**A**) for IVa. The intensity of NH bands was highly increased in the acid salts of I, III and V which may be due to protonation of tertiary nitrogen of the imidazole ring. It is interesting to note that a similar observation was recorded for IVa indicating the presence of NH^+ as shown in **A**.

The PMR (DMSO-d_6) spectral data were also in agreement with the assigned structures. The signal for the imidazole NH proton is found to undergo upfield shift from δ 8.15 to 7.9 with the interpolation of one more methylene group. On this basis the signal at δ 8.00 was assigned for the imidazole NH which is at a higher distance from $C_6H_5-CO-NH$- and the signal at δ 8.25 for the other NH proton in the case of V and VI. It may be noted that this correlation was also in agreement with the structure of IVa as assigned from IR and *pk** values.

Biological activity

The antibacterial screening of compounds against three microorganisms, viz. *Escherichia coli*, *Staphylococcus aureus* and *Bacillus megaterium*, was carried out employing agar-cup-plate diffusion method[1]. Twenty five ml of agar medium in a petridish of 10 cm diameter was inoculated with 0.15 ml suspension of 18 hr-old culture of the test organisms (10^9 cells/ml). Concentration of the test reagent in DMSO was 10 mg/ml and 0.1 ml of the solution was added to a cup of 8 mm diameter. After an incubation period of 36 hr, the zones of inhibition were measured. Compounds V and VI were found to be active against the gram +ve microorganisms *S. aureus* and *B. megaterium* and compound II was active against *B. megaterium*. But all were inactive against gram −ve bacteria *E. coli*. It is interesting to note that the sulphonamido derivatives of I, II, III and V were active against the gram −ve bacteria *E. coli*[1].

IR spectra in KBr matrices and PMR spectra in DMSO-d_6 were recorded. Dissociation constants of the benzoyl derivatives were determined by potentiometric titration in water-dioxane (1:1) at a

constant ionic strength (μ=0.5) at 20°C. Melting points were determined in open capillary tube and are uncorrected.

Preparation of benzamidobenzimidazoles (*I-VI*; *Table* 1)

Method (*A*)—An equimolar mixture of (0.05 mol each) N-benzoylamino acid and *o*-phenylenediamine (1:2 molar for synthesis of V) was fused at a suitable temperature (160°, 120°, 110° and 140° for the synthesis of I, II, III and V respectively) for 10 min. The reaction product was extracted with warm 1*N* hydrochloric acid (~40 ml), norited and filtered. The filtrate was cooled in ice-bath and *p*H of the solution adjusted to ~9 first by sodium hydroxide solution and then by dil. ammonia. The white compound thus separated was filtered, washed with water and recrystallised from aq. ethanol.

Method (*B*)—The same mixture (1:2 molar for the synthesis of VI) was refluxed in 4*N* hydrochloric acid (40 ml) for 2 hr (4 hr for compounds IV, V and VI). The *p*H of the solution was adjusted to ~9 and the compound collected and recrystallised as above.

The filtrate after separation of the compound V was acidified with gl. acetic acid to around *p*H 3 and left overnight at 5-10° when a white crystalline compound separated out. It was filtered, dissolved in dil. ammonia and reprecipitated with acetic acid and finally recrystallised from aq. DMSO to get white shining crystals. All the benzimidazoles were soluble in acetone, ethanol, DMF and DMSO and insoluble in water except compound IV which was insoluble in acetone and ethanol. The hydrochlorides of the benzimidazoles were prepared from acidic solution in acetone on evaporation.

Determination of dissociation constants

The dissociation constants of the benzoylamino acids and of the protonated benzamidobenzimidazoles (I-V) were determined by the method of Irving and Rossotti[12]. The *p*H values of the solutions, prepared in doubly distilled CO_2-free water and purified dioxane[13], were measured with a systronics *p*H meter having a glass electrodes (1-13 *p*H range) in conjunction with SCE connected to the cell by means of an agar-2*M* $NaNO_3$ bridge. Duplicate titrations were made in each case under identical conditions. Limits of error (Table 1) were determined by comparing the experimental formation curves with the calculated ones obtained by plotting the calculated $\bar{\eta}_H$ values against the experimental *p*H values[14].

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Synthesis of Some New Di-(5′-chloro-4′/2′-hydroxy-3′-chalconyl)methyl Ethers

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Synthesis of some new di-(5′-chloro-4′/2′-hydroxy-3′-chalconyl)methyl ethers (II and III) has been carried out by the Claisen-Schmidt condensation between di-(2-hydroxy-3/5-chloro-5/3-acetyl)benzylethers (Ia, Ib) and aryl aldehydes in the presence of ethanolic potassium hydroxide. In antifungal screening these compounds have been generally found to be stimulatory against *Penicillin notatum* at 100 ppm and 250 ppm concentrations.

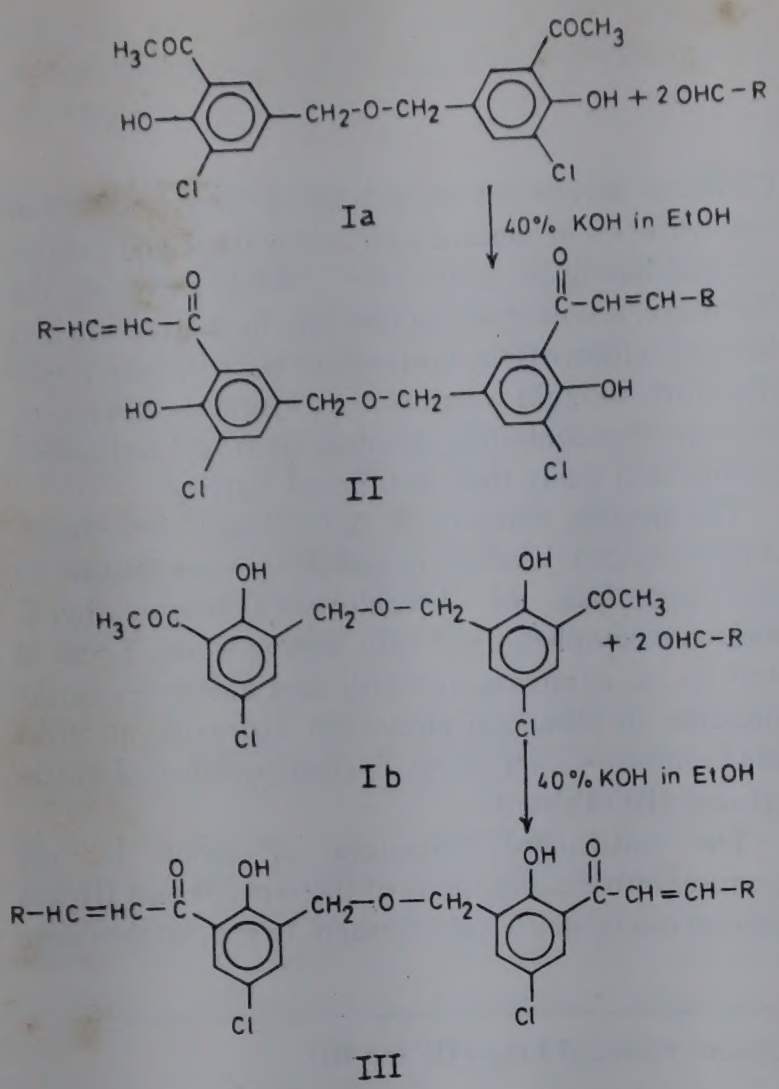
Chalcone derivatives are well known intermediates in the synthesis of heterocyclic compounds and exhibit various biological activities[1-5]. While surveying the literature, it was observed that very little attention had been paid towards the synthesis of bischalcones. It was therefore, thought worthwhile to synthesise some new bischalcones containing phenolic hydroxyl and chloro groups and study their antifungal activity.

The starting compounds di-(5/3-acetyl-3/5-chloro-2-hydroxy)benzyl ethers Ia and Ib were synthesised by the hydrolysis of 3/5-chloro-5/3-chloromethyl-2-hydroxyacetophenones[6] with boiling water. These Ia and Ib on condensation with aryl aldehydes in the presence of ethanolic potassium hydroxide afforded di-(5′-chloro-4′/2′-hydroxy-3′-chalconyl)methyl ethers (II and III) (Table 1).

The antifungal screening of some of the representative compounds of the types II and III was carried out by dry weight method. In general they were

Table 1—Characterization Data of Di-(chalconyl)methyl Ethers (II and III)

Compd	R	m.p. °C	Yield %	Crystallises from	Mol. formula	Found (%) (Cal.)		
						C	H	Cl
IIa	Phenyl	178	78	Benzene	$C_{32}H_{24}O_5Cl_2$	67.3 (67.2)	3.9 (4.2)	12.7 (12.4)
IIb	*o*-Chlorophenyl	183	70	Benzene	$C_{32}H_{22}O_5Cl_4$	61.5 (61.1)	3.1 (3.5)	22.6 (22.8)
IIc	*p*-Chlorophenyl	199	75	Benzene	$C_{32}H_{22}O_5Cl_4$	61.3 (61.1)	3.3 (3.5)	22.5 (22.8)
IId	*o*-Methylphenyl	171	70	AcOH	$C_{34}H_{28}O_5Cl_2$	69.7 (69.5)	4.2 (4.7)	12.5 (12.1)
IIe	*p*-Methoxyphenyl	198	68	AcOH	$C_{34}H_{28}O_7Cl_2$	65.4 (65.8)	4.3 (4.5)	11.7 (11.5)
IIf	*o*-Hydroxyphenyl	195	65	Benzene	$C_{32}H_{24}O_5Cl_2$	68.3 (68.6)	4.1 (4.2)	12.6 (12.7)
IIg	*m*-Hydroxyphenyl	200	70	Benzene	$C_{32}H_{24}O_5Cl_2$	68.5 (68.6)	4.3 (4.2)	12.5 (12.7)
IIh	*p*-Hydroxyphenyl	202	70	Benzene	$C_{32}H_{24}O_5Cl_2$	68.5 (68.6)	4.5 (4.2)	12.9 (12.7)
IIi	α-Naphthyl	215	65	AcOH	$C_{40}H_{28}O_5Cl_2$	72.7 (72.8)	4.6 (4.2)	11.4 (10.8)
IIIa	Phenyl	172	70	Benzene	$C_{32}H_{24}O_5Cl_2$	67.3 (67.2)	4.5 (4.2)	12.5 (12.4)
IIIb	*o*-Chlorophenyl	180	65	Benzene	$C_{32}H_{22}O_5Cl_4$	61.5 (61.1)	3.1 (3.5)	22.6 (22.8)
IIIc	*p*-Chlorophenyl	184	68	Benzene	$C_{32}H_{22}O_5Cl_4$	61.3 (61.1)	3.2 (3.5)	22.5 (22.8)
IIId	*o*-Methylphenyl	182	70	AcOH	$C_{34}H_{28}O_5Cl_2$	69.4 (69.5)	4.3 (4.7)	12.3 (12.1)
IIIe	*p*-Methoxyphenyl	191	65	AcOH	$C_{34}H_{28}O_7Cl_2$	65.3 (65.8)	4.1 (4.5)	11.9 (11.5)
IIIf	α-Naphthyl	212	67	AcOH	$C_{40}H_{28}O_5Cl_2$	72.5 (72.8)	4.6 (4.2)	10.9 (10.8)



found to be stimulatory against *Penicillin notatum* at 100 ppm and 250 ppm concentrations.

Melting points are uncorrected. IR spectra in nujol mull were recorded on a Perkin-Elmer infracord (ν_{max}, cm^{-1}), and PMR spectra in $CDCl_3$ on a varian T-60 spectrometer using TMS as internal reference (chemical shifts in δ, ppm).

Di-(5/3-acetyl-3/5-chloro-2-hydroxy)benzyl ethers: General Procedure

3/5-Chloro-5/3-chloromethyl-2-hydroxy-acetophenone (20 g, 0.1 mole) was refluxed with distilled water (100 ml) for 5 to 6 hr and the solution filtered while hot. The insoluble residue was refluxed with a fresh portion of water (25 ml) until no crystals of the reacting acetophenone separated out after cooling. The water insoluble residue remained after removal of the above compound was crystallised from *m*-xylene in white needles. Following compounds were prepared.

Ia: m.p. 169°, yield 10% (Found: C, 56.5; H, 4.4; Cl, 18.6. $C_{18}H_{16}O_5$ requires C, 56.4; H, 4.7; Cl, 18.5%).

Ib: m.p. 170°, yield 15% (Found: C, 56.4; H, 4.3; Cl, 18.3. $C_{18}H_{16}O_5$ requires C, 56.4; H, 4.7; Cl, 18.4%); IR: 1650-1670 (C=O), 1080-1100 (C−O−C, asymmetrical stretchings); PMR: 3.63 (6H, *s*, two $COCH_3$), 4.43 (4H, *s*, two CH_2-), 7.57-7.76 (4H, *m*, Ar-H) and 12.8 (2H, *s*, two OH, partially exchangeable with D_2O).

Di-(5'-chloro-4'/2'-hydroxy-3'-chalconyl)methyl ethers (II and III): General Procedure:

To an equimolar mixture of di-(5/3-acetyl-3/5-chloro-2-hydroxy)benzyl ether (Ia or Ib) and appropriate aryl aldehyde in ethanol (60 ml) was added 40% KOH (20 ml) in portions. The flask was corked and kept at room temperature for 12 hr. The contents of the flask were then acidified with dil. hydrochloric acid and poured over ice cold water. The solid obtained was filtered, washed with water, dried and crystallised from an appropriate solvent (Table 1).

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